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Health and Environmental Effects Profile for Chloroethene

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE
FOR CHLOROETHENE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
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16. ABSTRACT

The Health and Environmental Effects Profile for chloroethene was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Chloroethene has been evaluated as a carcinogen. The human carcinogen potency factor (q_1^*) for chloroethene is 1.9 $(mg/kg/day)^{-1}$ for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for chloroethene is 100.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1984.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1* (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

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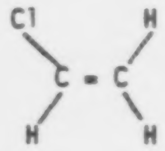
LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
bw	Body weight
CAS	Chemical Abstract Service
CNS	Central nervous system
CS	Composite score
K_{oc}	Soil sorption coefficient
K_{ow}	Octanol/water partition coefficient
MED	Minimum effective dose
MVC	Monovinyl chloride
ppb	Parts per billion
ppm	Parts per million
ppt	Parts per trillion
PVC	Polyvinyl chloride
RQ	Reportable Quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
TLV	Threshold limit value
VCM	Vinyl chloride monomer
WS	Water solubility

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Chloroethene may be more commonly known by the chemical name vinyl chloride. Other synonyms for chloroethene include chloroethylene, vinyl chloride monomer (VCM), monovinyl chloride (MVC), and ethylene monochloride (Verschueren, 1983). The structure for chloroethene is:



The molecular weight for chloroethene is 62.50 and the empirical formula is C_2H_3Cl. The CAS Registry number is 75-01-4.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Chloroethene is a colorless gas at normal temperatures and pressures with a mild, sweetish odor (Verschueren, 1983). It is soluble in hydrocarbons, oil, alcohol, chlorinated solvents, and most common organic solvents (Cowfer and Magistro, 1983). Selected physical properties of chloroethene are listed below:

Melting point:	-153.8°C	Cowfer and Magistro, 1983
Boiling point (1 atm):	-13.4°C	Cowfer and Magistro, 1983
Specific gravity:	0.9121 (15/4°C)	Verschueren, 1983
Refractive index:	1.3700 (20°C)	IARC, 1979
Vapor pressure:		
at 25°C	2660 mm Hg	Verschueren, 1983
at 20°C	2320 mm Hg	Carassiti et al., 1978
at 0°C	1230 mm Hg	Cowfer and Magistro, 1983

Log octanol/water partition coefficient:	0.6 (calculated) 1.2 (calculated)	Callahan et al., 1979 Mabey et al., 1981
Water solubility at 25°C:	2763 mg/ℓ	Horvath, 1982
Conversion factors (air):	1 mg/cm³=0.39 ppm 1 ppm=2.60 mg/cm³	Verschueren, 1983

Horvath (1982) has reviewed the available literature data regarding the solubility of chloroethene in water. The experimental results have been shown to vary considerably. The recommended value has been given above.

Chloroethene polymerizes in light or in the presence of a catalyst (IARC, 1979).

1.3. PRODUCTION DATA

The current domestic industrial manufacturers of chloroethene are listed in Table 1-1 along with their respective locations and annual capacities. In 1982 and 1983, U.S. production of chloroethene was reported to be 5.97 and 6.88 billion pounds (USITC, 1984).

Chloroethene is industrially produced by the pyrolysis of ethylene dichloride (Cowfer and Magistro, 1983) as shown:

$$2ClCH_2CH_2Cl \rightarrow 2CH_2 = CHCl + 2HCl$$

The ethylene dichloride is formed by either the direct chlorination of ethylene or by the oxychlorination of ethylene (Cowfer and Magistro, 1983).

1.4. USE DATA

Chloroethene has the following use pattern (CMR, 1983):

Polyvinyl chloride (PVC)	85%
Miscellaneous (mostly copolmer use)	1.5%
Export	13.5%

TABLE 1-1

United States Manufacturers of Chloroethene*

Manufacturer	Location	Annual Capacity (millions of pounds)
Borden Chem.	Geismar, LA	610
Dow	Oyster Creek, TX	750
	Plaquemine, LA	1250
DuPont (Conoco)	Lake Charles, LA	700
Formosa Plastics	Baton Rouge, LA	300
	Point Comfort, TX	530
Georgia-Pacific	Plaquemine, LA	1000
BF Goodrich	Calvert City, KY	1000
	La Porte, TX	1000
PPG Industries	Lake Charles, LA	900
Shell Chem.	Deer Park, TX	840
	Norco, LA	700
	TOTAL	9580

*Source: SRI, 1984

Limited quantities of chlorethene were used in the United States as an aerosol propellant in pesticide aerosol products and in self-pressurized household containers and as an ingredient of drug and cosmetic products (IARC, 1979). However, these uses are no longer in practice. Nearly all of the chloroethene consumed in the United States is used for the production of polyvinyl chloride or other polymers.

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

The individual fate processes, pertaining to chloroethene, are discussed below with respect to water, air and soil. Evaporation from water and photooxidation in the atmosphere appear to be the major chloroethene fate processes in aquatic and atmospheric media, respectively.

2.1. WATER

2.1.1. Hydrolysis. Based on results obtained from studies of chloroethene levels in samples of clarifer effluent from a chloroethene plant stored at 50°C for 57 hours at pH 4.3, 8.0 and 9.4 in sealed septum vials, Callahan et al. (1979) reported that chloroethene hydrolysis over a pH range of 4.3-9.4 does not appear to be environmentally important. Mabey et al. (1981) also reported that chloroethene hydrolysis is not environmentally significant. The hydrolytic half-life of chloroethene has been estimated to be <10 years at 25°C (Hill et al., 1976).

2.1.2. Oxidation. Experimental results show that chloroethene will not be significantly degraded by molecular oxygen at temperatures and oxygen concentrations present in natural waters (Hill et al., 1976); however, experiments at 85°C have shown that chloroethene is degraded by hydroxyl radicals (Hill et al., 1976). The rate constant for the reaction between chloroethene and hydroxyl radicals in aqueous solution at room temperature is about 7.3×10^{9} M^{-1} sec^{-1} (Guesten et al., 1981); assuming an average $\cdot OH$ concentration of 10^{-17} M in natural water, a half-life of ~110 days is calculated.

An estimated rate constant of 3 M^{-1} hr^{-1} for oxidation of chloroethene by $RO_2\cdot$ (peroxy radical) (Mabey et al., 1981) suggests that this reaction has no environmental significance. The importance of reaction with singlet oxygen cannot be evaluated because of the lack of rate constant data.

2.1.3. **Photolysis.** Chloroethene in water does not absorb ultraviolet radiation above 218 nm (Hill et al., 1976), therefore, direct photolysis in the aquatic environment is not expected to occur. As an experimental confirmation, Hill et al. (1976) exposed solutions of 10 ppm chloroethene in water to filtered light >300 nm from a mercury lamp; no photolysis occurred over a 90 hour period.

Hill et al. (1976) also experimentally studied the photosensitized photolysis of chloroethene in water. Chloroethene decomposed rapidly when irradiated with ultraviolet light in the presence of acetone (a high energy triplet sensitizer) or hydrogen peroxide (a free radical source). Since a high-energy sensitizer is required for effective photolysis, the ability of chloroethene to undergo photosensitized photolysis in natural waters is not certain. Various humic substances may be effective photosensitizers. Polyvinyl chloride plants are likely to use small amounts of peroxides in their polymerization processes. As a result, aqueous effluents containing both chloroethene and peroxides may be susceptible to sunlight-induced decomposition (Hill et al., 1976).

2.1.4. **Microbial Degradation.** The limited amount of existing data indicates that chloroethene is resistant to microbial degradation. Hill et al. (1976) found that an isolated bacterial culture containing two species of bacteria and three mixed fungal populations was unable to biodegrade chloroethene over a 5-week period at concentrations of 20-120 mg/ℓ. Helfgott et al. (1977) observed no degradation of chloroethene at 20°C over a 5-50 day period using an acclimated sewage seed as a microbial inoculum.

2.1.5. Other Reactions. It is possible, though not proven experimentally, that in an environment such as a municipal water chlorination, chloroethene may be converted to more highly chlorinated compounds based on the reactivity of carbon-carbon double bonds with chlorine and hypohalous acid (Hill et al., 1976).

Many salts have the ability to form complexes with chloroethene and can increase its water solubility. Therefore, the presence of salts in natural waters may significantly influence the amount of chloroethene remaining in the water (Callahan et al., 1979).

2.1.6. Transport.

2.1.6.1. **VOLATILIZATION** -- The available data indicates that chloroethene will evaporate rapidly from the aquatic environment. Scherb (1978) measured the evaporation half-life of chloroethene from a flowing channel and found it to be ~1-4 hours with a slight dependence on weather conditions. Turbulent flow increased the evaporation rate.

Dilling et al. (1975) experimentally measured the evaporation rate of chloroethene (1 ppm) from an open container containing 200 mℓ solution (65 mm depth) at 25°C while being stirred at 200 rpm. An initial half-life of 26 minutes was determined with 90% evaporation in 96 minutes. In a subsequent study (Dilling, 1977), a half-life of 27.6 minutes was obtained for 0.89 ppm chloroethene in water under the same experimental conditions. While the results of these experiments cannot be extrapolated directly to the aquatic environment, they do demonstrate the volatility of chloroethene in dilute aqueous solution.

McConnell et al. (1975) have experimentally determined the unitless Henry's Law Constant for chloroethene at 10°C to be 50; this converts to a Henry's Law Constant of 1.2 atm-m^3/mole. This value of Henry's Law

Constant indicates that volatilization is both significant and rapid from all bodies of water (Lyman et al., 1982). In addition, Lyman et al. (1982) have calculated the Henry's Law Constant for chloroethene at 20°C to be 2.4 atm-m^3/mole which the authors used to calculate an evaporation half-life of 2.5 hours from a stream 1 m deep, moving 1 m/sec with a wind current of 3 m/sec.

While Mabey et al. (1981) have theoretically calculated the reaeration rate ratio of chloroethene to be 0.675 at 25°C, Hill et al. (1976) have experimentally measured the ratio to be ~2. Assuming the oxygen reaeration rates from a typical pond, river and lake are 0.008, 0.04 and 0.01 hr^{-1} (Mabey et al., 1981), respectively, and a reaeration ratio of 2, the following chloroethene evaporation half-lives are calculated:

pond	43.3 hours
river	8.7 hours
lake	34.7 hours

2.1.6.2. **ADSORPTION** -- No experimental data were found in the available literature as cited in the Appendix regarding sorption of chloroethene to particulate matter and sediment in water. The calculated octanol/water partition coefficients for chloroethene (Section 1.2.) suggest adsorption may not be significant. Hill et al. (1976) have suggested that aquatic sediments could exhibit long-term storage of low levels of chloroethene if extreme environmental conditions, such as continual high levels of chloroethene input, were present.

2.1.6.3. **BIOACCUMULATION** -- Lu et al. (1977) examined the bioaccumulation of ^{14}C-chloroethene in a closed model aquatic ecosystem during a 3-day period. The high volatility of chloroethene minimized any potential bioaccumulation; however, relatively low tissue concentrations found in fish suggested that chloroethene is not biomagnified to any substantial degree.

The BCF of an organic chemical can be esti- mated from the K_{ow} or WS by use of the following regression equations:

$$\text{Log BCF} = 0.76 \text{ Log } K_{ow} - 0.23 \qquad \text{Veith et al., 1980} \qquad (2\text{-}1)$$

$$\text{Log BCF} = 2.791 - 0.564 \text{ Log WS (in ppm)} \qquad \text{Kenaga and Goring, 1978} \qquad (2\text{-}2)$$

Assuming, from Section 1.2., that Log K_{ow} is ~0.9 and that WS is 2763 ppm, the BCFs calculated from Equations 2-1 and 2-2 are 2.8 and ~7, respectively, indicating little importance of bioaccumulation in aquatic organisms.

2.2. AIR

2.2.1. Chemical Decomposition. The atmospheric chemical removal processes include reaction with hydroxyl radicals, reaction with other radicals, reaction with ozone and photolytic transformations (Cupitt, 1980). Table 2-1 contains available rate constants for the reaction of chloroethene with hydroxyl radicals, oxygen atoms [$O(^3P)$], and ozone along with calculated half-lives. Reaction with hydroxyl radicals appears to be the major removal mechanism for chloroethene in the atmosphere. The products of OH reaction with chloroethene are HCl, formaldehyde, formyl chloride, CO, CO_2, chloroacetaldehyde, acetylene, chloroethylene epoxide, chloroacetylchloranil, and H_2O (Woldbaek and Klaboe, 1978; Kagiya et al., 1975; Muller and Korte, 1977). A relatively high reactivity of chloroethene has also been demonstrated in smog chamber studies in which chloroethene and nitrogen oxides were irradiated with sunlamps and black lights (Carassiti et al., 1978; Dilling et al., 1976; Gay et al., 1976; Kanno et al., 1977; Cox et al., 1974).

Chloroethene in vapor-phase does not absorb light of wavelengths >220 nm (Fujimoto et al., 1970; Hill et al., 1976); therefore, direct photolysis will not occur in the atmosphere.

TABLE 2-1

Chloroethene Reaction Rates Constants for Gas-Phase Reactions

Chloroethene Reaction with	Rate Constant	Temperature (°C)	Calculated Half-life* (days)	Reference
•OH	4.5×10^{-12} cm³/molecule-sec	23	1.8	Howard, 1976
•OH	6.6×10^{-12} cm³/molecule-sec	26.2	1.2	Perry et al., 1977
•OH	5.6×10^{-12} cm³/molecule-sec	27	1.4	Cox et al., 1974
O (^{3}P)	5.98×10^{-13} cm³/molecule-sec	25	532	Atkinson and Pitts, 1977
O (^{3}P)	8.6×10^{-13} cm³/molecule-sec	25	373	Sanhueza and Heicklen, 1975
O_3	2.45×10^{-19} cm³/molecule-sec	25	33	Zhang et al., 1983
O_3	1.2×10^{6} cm³/mole-sec	27	4.2	Lyman et al., 1982

*Assuming average atmospheric concentrations of 10^6 molecules/cm³ for •OH; 2.5×10^4 molecules/cm³ for O (^{3}P); 1×10^{12} molecules/cm³ or 1.6×10^{-12} moles/cm³ for O_3

2.2.2. **Physical Removal.** The physical atmospheric removal mechanisms include dissolution (wet deposition), adsorption on aerosol particulates and dry deposition (Cupitt, 1980). These physical removal processes are not expected to be significant compared with the chemical removal processes.

2.3. SOIL

No experimental data could be found concerning the microbial or chemical degradation of chloroethene in soil as cited in the Appendix.

Experimental data were also not located concerning the adsorption of vinyl chloride to soil. The K_{oc} of an organic chemical can be estimated from its WS or K_{ow} by use of the following regression equations developed by Kenaga and Goring (1978):

$$\text{Log } K_{oc} = 3.64-0.55 \text{ Log WS (in ppm)} \qquad (2\text{-}3)$$

$$\text{Log } K_{oc} = 0.544 \text{ Log } K_{ow} + 1.377 \qquad (2\text{-}4)$$

Assuming, from Section 1.2., that WS is about 2763 ppm and Log K_{ow} is ~0.9, the K_{oc} values calculated from Equations 2-3 and 2-4 are 56 and 74, respectively, indicating a high soil mobility. Prediction of K_{oc} from the molecular topology and quantitative structure-activity relationship analysis method of Sabljic (1984) yields a K_{oc} value of 17, again indicating high soil mobility.

The high vapor pressure of chloroethene suggests that evaporation from soil will occur rapidly. Jury et al. (1984) predicted that the effective half-life (due to volatilization) of chloroethene placed 10 cm deep in dry soil will be only 12 hours. The presence of water, which may result in transporting chloroethene deeper in soil, may lengthen the half-life.

2.4. SUMMARY

The primary loss process for chloroethene released into water is evaporation into the atmosphere. For a variety of natural waters the half-life for this process would be expected to take hours to days. In waters containing appropriate photosensitizers, which may include humic substances, photodegradation may occur fairly rapidly. Chemical hydrolysis and oxidation of chloroethene in water are not expected to be environmentally important. Limited microbial data suggests that chloroethene is resistant to microbial degradation. Chloroethene is not expected to bioaccumulate significantly in aquatic organisms.

Chloroethene reacts in the troposphere with photochemically produced hydroxyl radicals with a half-life of 1.2-1.8 days under average conditions. In photochemical smog situations, the half-life would be reduced to a few hours.

Chloroethene can be expected to volatilize quite rapidly from soil. Some leaching of choloroethene from soil into groundwater is expected to occur.

3. EXPOSURE

3.1. WATER

Exposure of chloroethene to the aquatic environment can result from wastewater releases generated by manufacturing of the chemical and use of the chemical to produce polyvinyl chloride and other products. The source of chloroethene in potable water is the leaching of unreacted monomer from polyvinyl chloride transmission pipes (Fishbein, 1979; Ando and Sayato, 1984; Banzer, 1979; Nakamura and Mimura, 1977).

Westrick et al. (1984) reported the results of the U.S. EPA's Groundwater Supply Survey conducted by the Office of Drinking Water in which 945 water supplies throughout the United States were measured for volatile organic compounds. Chloroethene was detected in 7 of the 945 waters analyzed at a maximum concentration of 8.4 µg/ℓ and a median concentration (in positive samples) of ~2.6 µg/ℓ. Cole et al. (1984) have reported the preliminary findings from the U.S. EPA's Nationwide Urban Runoff Program (NURP) in which priority pollutants were monitored in urban stormwater runoff; chloroethene was not detected in any samples from 15 reporting cities.

Chloroethene has been detected in drinking water in Miami, FL and Philadelphia, PA at approximate concentrations of 5.6 and 0.27 µg/ℓ, respectively (U.S. EPA, 1975). A level of 50 ppb chloroethene were detected in drinking water wells in Long Island, NY (Burmaster, 1982). Data from nine states in the United States indicated that chloroethene was detected in 7% of wells and surface waters tested with a maximum groundwater concentration of 380 µg/ℓ (Dyksen and Hess, 1982). Coniglio et al. (1980) has summarized available chloroethene monitoring data from over 100 United States cities' surface and groundwaters which were analyzed; chloroethene was found in raw surface water (7.6% positive), finished surface water

(2.3% positive), raw groundwater (15.4% positive) and finished groundwater (4.0% positive) at levels of 0.1-9.8 μg/ℓ.

The gross analysis available from the U.S. EPA STORET Data Base reports the following data regarding chloroethene:

Water	Sediment	Fish Tissue	
No. observations	5553	649	530
Max. concentration	202,662 μg/ℓ	580 μg/kg	250 mg/kg
Min. concentration	0	0	0
Median concentration	107 μg/ℓ	23 μg/kg	6 mg/kg

Chloroethene has been detected in wells from a speciality product plant in Sanborn, NY that manufactures graphite cloths (Pfaudler Co., 1984). The source of chloroethene is evidently the trichloroethylene used as a solvent in the plant. Two active wells in this area showed chloroethene concentrations of 7 and 28 ppb. Groundwater obtained as a result of several soil borings in this area contained chloroethene at concentrations varying from none detected to 79 ppb.

3.2. FOOD

Small quantities of chloroethene can be exposed to food by migration of chloroethene monomer present in polyvinyl chloride food wrapings and containers (Gilbert et al., 1980). The U.S. Food and Drug Administration has found that up to 20 mg/kg (ppm) chloroethene may be present in alcoholic beverages packaged in polyvinyl chloride containers (IARC, 1979). In 1973, the United States Treasury Department banned the use of chloroethene polymers for packaging alcoholic beverages (IARC, 1979). In addition to alcoholic beverages, chloroethene has been detected in vinegar packaged in these containers at levels up to 9.4 mg/kg (IARC, 1979).

3.3. INHALATION

Chloroethene is emitted to the atmosphere at both chloroethene production facilities and polyvinyl chloride production plants (Graedel, 1978; Fishbein, 1979; Bertram, 1977). In addition, chloroethene is emitted to air in gases released from sanitary landfills (Bruckman and Muelder, 1982; Graedel, 1978), in emissions resulting from the thermal degradation of polyvinyl chloride (Wakeman and Johnson, 1978), and in tobacco smoke (Graedel, 1978). The U.S. EPA estimated that prior to 1975, in excess of 100 million kg/year of chloroethene escaped to the atmosphere in the United States from polyvinyl chloride production facilities and that the average chloroethene concentration in the air around these plants was 17 ppb (IARC, 1979; Fishbein, 1979).

Harkov et al. (1983) detected only trace amounts of chloroethene in 3/113 samples of general urban air analyzed from Newark, Elizabeth, and Camden, NJ during July-August 1981. Subsequent monitoring of 105 air samples from the same cities during January-February 1982 detected no chloroethene (Harkov et al., 1984). Bozzelli and Kebbekus (1979) found an average chloroethene concentration of 3.4 ppb in 11 positive samples taken in East Rutherford, NJ in 1978 that showed detectable levels of chloroethene; Bozzelli et al. (1980) found an average concentration of 0.4 ppb in six air samples that showed detectable levels of chloroethene (73 total samples). The samples were collected from six urban New Jersey areas.

McMurry and Tarr (1978) detected chloroethene in 29% of 62 air samples taken in the vicinity of production and use facilities near Channelview, TX; maximum concentration detected was 13 ppb. Gordon and Meeks (1977) found chloroethene levels of 3.1-1250 ppb in Houston, TX air during June-July, 1974; large production and use facilities are located in the area. Chloroethene has been detected in the air of Delaware City, DE at an average concentration of 790 ppb (Lillian et al., 1975). Pellizzari (1977) found chloroethene concentrations of 400-120,000 ng/cm^3 in a few air samples from New Jersey; Pellizzari (1978) and Pellizzari et al. (1979) have also detected chloroethene in air samples from various industrialized United States locations. Gay and Noonan (1975) detected chloroethene concentrations of 40 ppb in a residential Niagara Falls area near a chloroethene plant, 28 ppb downwind from the plant and 0 ppb upwind from the plant.

Grimsrud and Rasmussen (1975) analyzed the air in the rural Northwest U.S.A. and did not detect chloroethene above the detection limit of 5 ppt.

The air inside two new automobiles was found to contain 0.4-1.2 ppm chloroethene (Hedley et al., 1976); the chemical was thought to have volatilized from plastics in the automobile interiors.

3.4. DERMAL

Pertinent monitoring data were not located in the available literature as cited in the Appendix.

4. PHARMACOKINETICS

The pharmacokinetics on chloroethene have been reviewed by the U.S. EPA (1980, 1984a), Vainio (1978), Dietz et al. (1983) and Bolt et al. (1981).

4.1. ABSORPTION

Gastrointestinal absorption of chloroethene in rats occurs rapidly following ingestion of aqueous or vegetable oil treatment solutions (Withey, 1976). Maximum blood levels were reached within 10-20 minutes of dosing with aqueous (22.6 or 28.2 mg/rat) or vegetable oil (12.53 or 25.1 mg/rat) chloroethene solutions. Quantitatively, absorption of chloroethene (in PVC powder) from the gastrointestinal tract of rats was ~83-92% based on fecal recovery (Feron et al., 1981).

Absorption of chloroethene from the lungs following inhalation exposure occurs rapidly with blood levels equilibrating to atmospheric levels within a short period (Watanabe et al., 1976b; Withey, 1976; Duprat et al., 1977; Bolt et al., 1977). Withey (1976) reported that equilibrium blood levels in rats were reached within 30 minutes of exposure at levels up to 7000 ppm. Similarly, Bolt et al. (1977) reported that blood levels reached an equilibrium within ~15 minutes following inhalation of chloroethene. In human volunteers, 42% of inhaled chloroethene was retained by the lungs (Krajewski et al., 1980). Absorption efficiency did not appear to be affected by exposure at 7.5-60 mg/m^3. Individual variation, however, was high with mean retention values after 6 hours exposure at 30 mg chloroethene/m^3 ranging from 30-71% among five volunteers.

Hefner et al. (1975a) reported that percutaneous absorption of chloroethene was 0.031 and 0.023% of the available compound in rhesus monkeys exposed (excluding head) at 800 and 7000 ppm (2045 and 17,894 mg/m^3) for 2.5 and 2.0 hours, respectively.

4.2. DISTRIBUTION

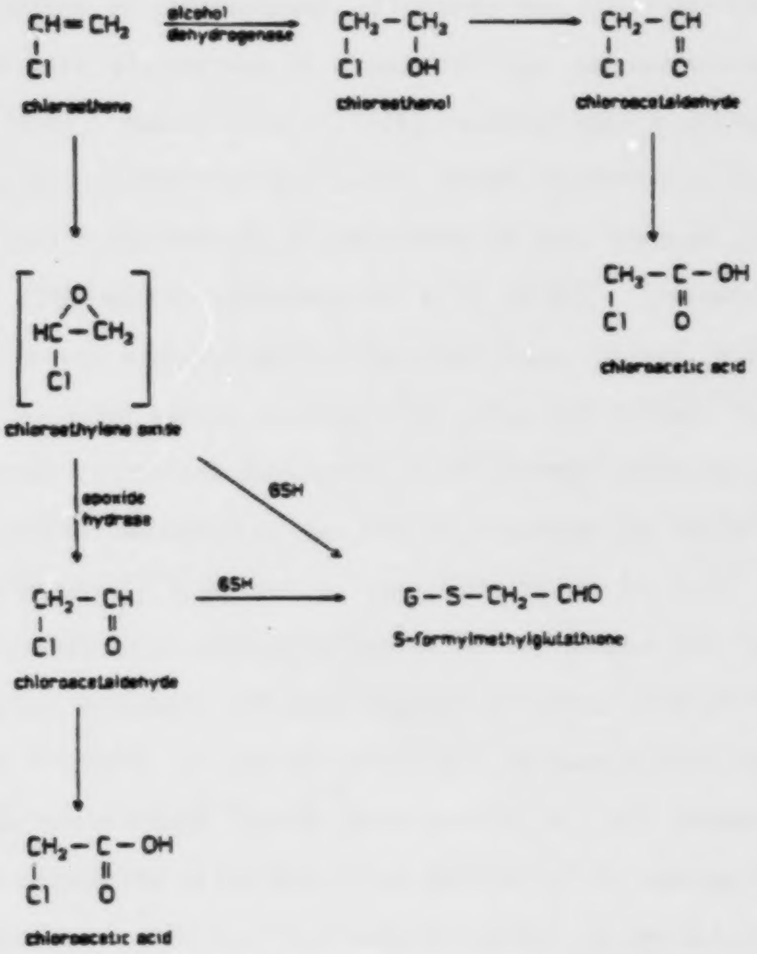
The distribution of chloroethene and/or its metabolites following oral exposure was studied by Watanabe et al. (1976a). Rats were given single oral doses of ^{14}C-chloroethene by gavage at 0.05, 1.0 or 100.0 mg/kg and the amount remaining in the body was determined after 72 hours. The liver contained the most radioactivity at all dose levels (up to 3 times that in other tissues) while the skin, lung, plasma, fat, carcass and muscle contained less in decreasing concentration.

The distribution of ^{14}C-chloroethene was determined in rats exposed by inhalation at 20,000 ppm (51,125 mg/m^3) for 5 minutes (Duprat et al., 1977). At 10 minutes after the exposure period radioactivity was detected in the liver, bile duct, digestive tract and kidneys. At 3 hours after exposure radioactivity was also detected in the urinary tract, salivary and lacrimal glands, thymus and skin. Watanabe et al. (1976b) determined tissue levels of radioactivity in rats exposed by inhalation to 10 or 1000 ppm (26 or 2556 mg/m^3) ^{14}C-chloroethene for 6 hours. At 72 hours after exposure, radioactivity was detected in the liver, kidney, skin, lung, muscle, carcass, plasma and fat in decreasing concentration. Immediately after a 5-hour inhalation exposure at 50 ppm (128 mg/m^3) ^{14}C-chloroethene, tissue levels of radioactivity, expressed as % incorporated/g tissue, were highest in the kidney (2.13%) and liver (1.86%) with lower levels in the spleen (0.73%) and brain (0.17%) (Bolt et al., 1976). Radiolabeled compounds (probably as metabolites) were still detectable in these tissues 48 hours after exposure was started. In a German study (Buchter et al. 1977), radioactivity from labeled chloroethene was concentrated in the adipose tissue with lesser amounts in blood, liver, kidney, muscle and spleen when its metabolism was blocked using 6-nitro-1,2,3-benzothiadiazole. When metabolism was not blocked, highest levels of radiolabeled metabolites were detected in the liver and kidney.

4.3. METABOLISM

Metabolism of chloroethene occurs primarily by oxidation by hepatic microsomal enzymes. The toxicity and mutagenicity of chloroethene are regarded as attributable to its oxidized metabolites (U.S. EPA, 1984a). Two metabolism schemes have been suggested, one involving alcohol dehydrogenase, the other a mixed function oxidase system (Figure 4-1) (Bartsch and Montesano, 1975). Henschler and Bonse (1977) reported that chloroethene is oxidized to an epoxide and further to the aldehyde. The unsymmetrical and unstable epoxide intermediate, chloroethylene oxide, is thought to be responsible for the mutagenic potential of chloroethene (Section 5.2.) (Gwinner et al., 1983). Unmetabolized chloroethene does not appear to be mutagenic (Section 5.2.).

In human liver specimens chloroethene was metabolized by aryl hydrocarbon hydrolylase enzymes at a rate ~84% that of rat liver preparations (Sabadie et al., 1980). _In_ _vitro_ metabolism of chloroethene with human liver preparations resulted in electrophilic metabolites which were mutagenic to _Salmonella_ _typhimurium_ (TA1530 and TA100). Jaeger et al. (1974) reported that pretreatment of rats with phenobarbital enhanced hepatic metabolism of chloroethene; Hultmark et al. (1979) reported no effect of phenobarbital, but pyrazole (alcohol dehydrogenase inhibitor) and ethanol treatment inhibited metabolism of chloroethene. Metabolic activity was localized in hepatic microsomes and was NADPH-dependent, suggesting that the metabolizing enzyme is a cytochrome p450 (Hultmark et al., 1979). These data suggest that both pathways of metabolism occur. Hefner et al. (1975a)



alcohol dehydrogenase
chloroethene
chloroethanol
chloroacetaldehyde
chloroacetic acid
chloroethylene oxide
epoxide hydrase
GSH
GSH
G—S—CH₂—CHO
S-formylmethylglutathione
chloroacetaldehyde
chloroacetic acid

FIGURE 4-1

Metabolic Pathways of Chloroethane

suggested that the alcohol dehydrogenase pathway predominated at low exposure levels (saturable at 105-220 ppm or 268-562 mg/m³) and others predominate at higher levels.

Metabolites of chloroethene, chloroethylene oxide and chloroacetaldehyde can react with glutathione or other cellular macromolecules (Watanabe and Gehring, 1976). Kappus et al. (1976) reported that a metabolite of chloroethene, probably chlorethylene oxide, bound irreversibly to liver proteins. Hepatic glutathione content was decreased in rats exposed to chloroethene at $\geq$100 ppm (256 mg/m³) (Watanabe et al., 1978a). Irreversible binding to proteins in the kidney, small intestine, lung, spleen, muscle and albumin occurs to a lesser extent than in liver (Bolt and Filser, 1977). Guengerich and Watanabe (1979) and Guengerich et al. (1981) reported covalent binding of radioactive metabolites of ^{14}C-chloroethene to proteins and nucleic acids following in vivo and in vitro treatment in rats. Gwinner et al. (1983) reported that chloroethylene oxide was responsible for alkylation of DNA, causing mutagenic and carcinogenic effects; chloroacetaldehyde apparently has little or no similar activity. Hathway (1977), however, reported that chloroacetaldehyde caused depurination of calf thymus DNA suggesting that this metabolite could also alter DNA and elicit oncogenic effects.

Metabolism of inhaled chloroethene appears to be saturable at ~220-250 ppm (562-639 mg/m³) with a metabolic rate (V_{max}) of 110 µmol/hour/kg bw in rats (Bolt et al., 1977; Filser and Bolt, 1979; Hefner et al., 1975b). During the initial phase of metabolism, when alcohol dehydrogenase metabolism may predominate, a $t_{1/2}$ of 86 minutes was determined, while a slower rate, $t_{1/2}$ of 261 minutes occurred during the second, saturated stage of metabolism (Hefner et al., 1975b,c). The amount of chloroethene metabolized followed Michaelis-Menten kinetics (Gehring et al., 1978). Chloroethene metabolism in rhesus monkeys was also a dose-dependent, saturable process with first order kinetics below the saturation point of 200-300 ppm (511-767 mg/m³) (Buchter et al., 1980). A V_{max} of ~50 mmol/hour/kg bw in the rhesus monkey was suggested as a closer approximation of metabolism in man than that in rodents (10-fold higher rate than primates).

Watanabe et al. (1978b) conducted single-exposure and 7-week inhalation studies of chloroethene (5000 ppm or 12,781 mg/m³, 6 hours/day, 5 days/week) in rats to compare its metabolism after acute and repeated exposure. Based on the time course and routes of excretion, metabolism of chloroethene appeared to be the same following acute and repeated exposures. There was no evidence that chloroethene induced its own metabolism or increased the activity of several other hepatic enzymes. Binding of chloroethene or its metabolites to hepatic macromolecules was increased 20-25% in rats exposed repeatedly compared to rats treated for one exposure. Comparing continuous and intermittent acute exposure, Jedrychowski et al. (1984) reported that hepatic nonprotein sulfhydryl content was decreased in a dose-related manner over the exposure range of 15-15,000 mg chloroethene/m³ (time-weighted average concentrations) regardless of exposure schedule. Intermittent exposure at 500 or 15,000 mg/m³ (TWA) did result in less urinary thiodiglycolic acid excretion than continuous exposure.

4.4. EXCRETION

Elimination of chloroethene and its metabolites following oral ingestion has been studied in rats by Green and Hathway (1975), Watanabe and Gehring (1976) and Watanabe et al. (1976a). ^{14}C-chlorethene was administered in corn oil by gavage in both studies at dose levels of 0.25 and 450 mg/kg or 0.05, 1.0, and mg/kg, respectively. Elimination of radioactivity was monitored in the exhaled air (as chloroethene or carbon dioxide), urine and feces for 72 hours after dosing, at which time excretion was essentially complete. Watanabe and Gehring (1976) and Watanabe et al. (1976a) also determined residual radioactivity in the carcass after 72 hours. The excretion data following oral dosing reported in these studies are summarized in Table 4-1. These data show a clear trend toward increased exhalation of chloroethene and decreased urinary metabolites, CO_2 and fecal excretion at higher dose levels of chlorethene. Elimination of unchanged chloroethene by the lungs is usually complete within 3-4 hours while elimination of CO_2 and urinary metabolites is greatest during the first 24 hours but continues at low levels for several days. Urinary metabolites were identified as N-acetyl-S-(2-hydroxyethyl)-cysteine, thiodiglycolic acid, N-acetylS-(2-chloroethyl)-cysteine, chloroacetic acid and glutamic acid (Watanabe and Gehring, 1976; Green and Hathway, 1975).

The elimination of chloroethene and its metabolites following inhalation exposure appears to follow a similar pattern to that reported following oral ingestion. Watanabe and Gehring (1976) exposed rats to 10 or 1000 ppm (26 or 2556 mg/m^3) ^{14}C-chloroethene for 6 hours and measured elimination of radioactivity over a 72 hour period. Watanabe et al. (1978a,b) exposed rats to 5000 ppm (12,781 mg/m^3) ^{14}C-chloroethene for a single 6-hour exposure or for 6 hours following repeated subchronic exposure (5000 ppm, 6 hours/day, 5 days/week for 7 weeks) to non-labeled chloroethene. The elimination of radioactive compounds following inhalation exposure at different concentrations (Table 4-2) was similar to that following oral ingestion. Exhalation of unchanged chloroethene increased while urinary, fecal and carbon dioxide elimination decreased at higher exposure levels (see Table 4-2). Urinary metabolites were identified as N-acetyl (S-2-hydroxyethyl)cysteine, thiodiglycolic acid and possibly S-(2-hydroxyethyl)cysteine (Watanabe and Gehring, 1976).

TABLE 4-1

Percent of ^{14}C-Chloroethene Recovered During 72 Hours Following Single Oral Doses

	Dose (mg/kg)					
	0.05[a]	0.25[b]	1.0[a]	20[a]	100[a]	450[b]
Expired:						
as Chloroethene	1.43	3.7	2.13	41.6	66.64	91.9
as Carbon Dioxide	8.96	13.5	13.26	4.8	2.52	0.7
Urine	68.34	75.1	59.30	22.6	10.84	5.4
Feces	2.39	4.6	2.20	1.0	0.47	0.7
Carcass	10.13	NR	11.10	11.0	1.83	NR
Cage wash	0	NR	0.84	NR	0	NR
Total[c]	91.25	96.9	88.83	81.0	82.30	98.7

[a] Watanabe and Gehring, 1976

[b] Green and Hathway, 1975

[c] Percent of dose administered

NR = Not reported

TABLE 4-2

Percent[a] of ^{14}C-Chloroethene Recovered During 72 Hours Following Inhalation Exposure

	Concentration (ppm)			
	10[b]	1000[b]	5000[c]	5000[c,d]
Expired:				
as Chloroethene	1.61	12.26	54.5	53.7
as Carbon Dioxide	12.09	12.30	8.0	9.6
Urine	67.97	56.29	27.1	25.7
Feces	4.45	4.21	3.2	1.4
Carcass	13.84	14.48	7.3	9.7
Cage wash	0.15	0.23	NR	NR
Total recovered, µg	248	6642	25,670	24,070

[a] Percent of total recovered

[b] Watanabe and Gehring, 1976

[c] Watanabe et al., 1978a

[d] Treatment following repeated exposure to unlabeled chloroethene (6 hours/ day, 5 days/week for 7 weeks)

Exhalation of unchanged chloroethene following inhalation exposure in human volunteers represented 3.6-4.7% of the inhaled concentration (3, 6, 12 or 24 ppm (7.7, 15, 31 or 61 mg/m^3). Elimination by this route represented a minor portion of the absorbed dose and decreased to undetectable levels within ~30 minutes after exposure was terminated (Krajewski et al., 1980).

Green and Hathway (1975) have examined the elimination of radioactivity from ^{14}C-chloroethene following intraperitoneal and intravenous injection at 0.25 or 450 mg/kg. Following intraperitoneal injection at 0.25 mg/kg exhalation of unchanged chloroethene and CO_2 and urinary and fecal radioactivity accounted for 43.2, 11.0, 43.1 and 1.8% of the administered dose, respectively. At 450 mg/kg by intraperitoneal injection exhaled chloroethene, CO_2, urinary and fecal radioactivity accounted for 96.2, 0.7, 2.6 and 0.1% of the dose, respectively. Intravenous dosing at 0.25 mg/kg resulted in 99.0, 0.1, 0.5 and 0.1% of the dose recovered as unchanged exhaled chloroethene, CO_2, urinary and fecal compounds, respectively.

5. EFFECTS

5.1. CARCINOGENICITY

The carcinogenicity of chloroethene in animals has been well established by the numerous available studies. Several reviews of the available data on the carcinogenicity of chloroethene have been reported (Maltoni, 1977a; Vainio, 1978; IARC, 1979; Maltoni et al., 1982; U.S. EPA, 1983a; Tamburro, 1984; Kalmaz and Kalmaz, 1984; U.S. EPA, 1984a,b). Maltoni et al. (1980) prepared an extensive summary document of a series of carcinogenicity bioassays conducted on chloroethene between 1971-1977. Due to the abundance of data and the recent review documents on the carcinogenicity of chloroethene, this summary will emphasize recently reported bioassays and those studies useful for quantitative carcinogenic risk estimation.

In 1971, Viola et al. (1971) reported that chloroethene was carcinogenic, inducing skin carcinoma, lung carcinoma and osteochondroma, in Wistar rats exposed by inhalation at 30,000 ppm (76,687 mg/m^3), 4 hours/day, 5 days/week for 12 months (Table 5-1). Maltoni and coworkers (Maltoni and Lefemine, 1974, 1975; Maltoni, 1977b; Maltoni et al., 1980) reported liver angiosarcoma and renal nephroblastoma in Sprague-Dawley rats given chloroethene by gavage at 16.65 and 50 mg/kg (Table 5-2). In rats treated by inhalation an increased incidence of liver angiosarcoma occurred among groups treated at $\geq$100 ppm (256 mg/m^3) chloroethene and kidney nephroblastomas occurred among rats treated at 6000 and 10,000 ppm (15,337 and 25,562 mg/m^3) (see Table 5-2). Maltoni et al. (1980, 1981) exposed Sprague-Dawley rats, Swiss mice and golden hamsters to chloroethene by inhalation at levels of 1-30,000, 50-10,000 and 50-10,000 ppm (2.6-76,687, 128-25,562 and 128-25,562 mg/m^3), respectively, 4 hours/day, 5 days/week for 1 year (rats) or 30 weeks. Liver angiosarcoma and nephroblastoma occurred in rats

TABLE 5-1

Bioassay Data for Male Wistar Rats (Ar/IRE) Exposed to Chloroethene by Inhalation[a]

Dose or Exposure[b] (ppm)	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
30,000	12 months	>12 months[c]	99%	vapor/air	skin	epidermoid carcinoma	15/26
					lung	carcinoma	6/26
					bone	osteochondroma	5/26
0	NA	>12 months[c]	NA	air only	skin	epidermoid carcinoma	0/25
					lung	carcinoma	0/25
					bone	osteochondroma	0/25

QUALITY OF EVIDENCE

Strengths of Study: An appropriate route of administration was used. The chloroethene was relatively pure. Appropriate controls were included for comparison.

Weakness of Study: Only male mice were tested. The duration of the study could have been longer. No statistics were compiled on incidences between treated and untreated animals.

Overall Adequacy: Adequate

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[a] Source: Viola et al., 1971

[b] Exposure was for 4 hours/day, 5 days/week for 12 months.

[c] Surviving animals were killed at 20-day intervals following treatment.

NA = Not applicable

TABLE 5-2

Bioassay Data for Sprague-Dawley Rats Exposed to Chloroethene for 52 weeks[a,b]

Exposure Route	Sex	Dose or Exposure[c]	Duration of Study (weeks)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
Inhalation	NR	10,000 ppm	155	vapor/air	liver	angiosarcoma	9/60
					kidney	nephroblastoma	5/60
		6,000 ppm	155	vapor/air	liver	angiosarcoma	13/60
					kidney	nephroblastoma	4/60
		200 ppm	143	vapor/air	liver	angiosarcoma	12/120
		150 ppm	143	vapor/air	liver	angiosarcoma	5/120
		100 ppm	143	vapor/air	liver	angiosarcoma	1/120
		0 ppm	143-155	air only	liver	angiosarcoma	0/500
					kidney	nephroblastoma	0/120
Oral (gavage)	NR	50 mg/kg	136	olive oil	liver	angiosarcoma	16/80
					kidney	nephroblastoma	2/80
		16.65 mg/kg	136	olive oil	liver	angiosarcoma	9/80
					kidney	nephroblastoma	3/80

TABLE 5-2 (cont.)

Exposure Route	Sex	Dose or Exposure^c	Duration of Study (weeks)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
Oral (gavage) (cont.)	M,F	0.0 mg/kg	136	olive oil only	liver kidney	angiosarcoma nephroblastoma	0/150 0/150

QUALITY OF EVIDENCE

Strengths of Study: A broad range of dose levels were tested. Carcinogenic response was shown by two routes of administration. Duration of study was long in all cases.

Weakness of Study: No statistics were reported. The sex of test animals is not reported. Data for the control group for the gavage studies is reported in Maltoni et al., 1981. Animals treated by gavage. The purity of the chloroethene is not reported.

Overall Adequacy: Adequate

Comments: This study focused on different factors affecting the carcinogenic effect (animal species, strain and age, treatment duration, and exposure levels).

---

[a] Source: Maltoni, 1977b

[b] Purity of compound not reported

[c] Exposure to chloroethene by inhalation was for 4 hours/day, 5 days/week for 52 weeks; by gavage once daily in olive oil 4-5 days/week.

NR = Not reported

treated at levels ≥10 and ≥25 ppm (26 and 64 mg/m³), respectively, while no similar tumors were seen in lower-dose groups or controls (Table 5-3). In mice, liver angiosarcoma occurred among all treated groups and lung tumors were more prevalent among animals treated at ≥250 ppm (639 mg/m³) (see Table 5-3). Forestomach tumors (papillomas and acanthomas) were increased in a dose-related trend among golden hamsters inhaling chloroethene (see Table 5-3).

Lee et al. (1977a, 1978) reported an increased incidence of liver and lung hemangiosarcomas among groups of male and female CD rats exposed to chloroethene at 250 and 1000 ppm (639 and 2556 mg/m³), 6 hours/day, 5 days/week for 12 months (Table 5-4). Rats treated at 0 or 50 ppm (0 or 128 mg/m³) on this regimen developed no similar tumors. In male and female CD-1 mice treated at 50, 250 and 1000 ppm (128, 639 and 2556 mg/m³) chloroethene, 6 hours/day, 5 days/week for 12 months, an increased incidence of liver hemangiosarcomas and bronchioloalveolar adenomas occurred in a dose-related trend (see Table 5-4). Hong et al. (1981) tested the carcinogenic effect of inhaled chloroethene at 50, 250 or 1000 ppm (128, 639 or 2556 mg/m³), 6 hours/day, 5 days/week for exposure durations of 1, 3, or 6 months in mice or 6 or 10 months in rats. In rats, treatment at 250 or 1000 ppm (639 or 2556 mg/m³) for 6 or 10 months followed by a 12-month latency caused the development of hepatocellular carcinoma, bronchioalveolar tumors and hemangiosarcoma of the liver and lung (Table 5-5). Rats treated at 50 ppm (128 mg/m³) developed no similar tumors and one hepatocellular carcinoma occurred among a control-group rat. In mice the incidences of liver hemangiosarcoma and bronchioalveolar tumors were increased in a dose- and duration-related trend (see Table 5-5). Treatment at 250 and 1000 ppm (639

TABLE 5-3

Animal Bioassay Data for Inhalation Exposure to Chloroethene[a,b]

Species/ Strain	Sex	Dose or Exposure[c] (ppm)	Duration of Treatment (weeks)	Duration of Study (weeks)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
Rat/ Sprague-Dawley	M,F	30,000	52	68	air/vapor	liver kidney	angiosarcoma nephroblastoma	18/60 NR
		10,000	52	135	air/vapor	liver kidney	angiosarcoma nephroblastoma	7/60 5/60
		6,000	52	135	air/vapor	liver kidney	angiosarcoma nephroblastoma	13/59 5/59
		2,500	52	135	air/vapor	liver kidney	angiosarcoma nephroblastoma	13/60 6/60
		500	52	135	air/vapor	liver kidney	angiosarcoma nephroblastoma	6/60 6/60
		250	52	135	air/vapor	liver kidney	angiosarcoma nephroblastoma	3/59 5/59
		200	52	143	air/vapor	liver kidney	angiosarcoma nephroblastoma	12/120 7/120
		150	52	143	air/vapor	liver kidney	angiosarcoma nephroblastoma	6/119 11/119
		100	52	143	air/vapor	liver kidney	angiosarcoma nephroblastoma	1/120 10/120
		50	52	135	air/vapor	liver kidney	angiosarcoma nephroblastoma	1/60 1/60
		25	52	147	air/vapor	liver kidney	angiosarcoma nephroblastoma	5/120 1/120
		10	52	147	air/vapor	liver kidney	angiosarcoma nephroblastoma	1/119 0/119
		5	52	147	air/vapor	liver kidney	angiosarcoma nephroblastoma	0/119 0/119

TABLE 5-3 (cont.)

Species/ Strain	Sex	Dose or Exposure^c (ppm)	Duration of Treatment (weeks)	Duration of Study (weeks)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
Rat/ Sprague-Dawley	M,F	1	52	147	air/vapor	liver kidney	angiosarcoma nephroblastoma	0/118 0/118
		0	NA	135-147	air only	liver kidney	angiosarcoma nephroblastoma	0/363 0/363
Mouse/ Swiss	M,F	10,000	30	81	air/vapor	liver lung	angiosarcoma tumor	10/56 45/56
		6,000	30	81	air/vapor	liver lung	angiosarcoma tumor	13/60 47/60
		2,500	30	81	air/vapor	liver lung	angiosarcoma tumor	16/59 40/59
		500	30	81	air/vapor	liver lung	angiosarcoma tumor	14/60 50/60
		250	30	81	air/vapor	liver lung	angiosarcoma tumor	18/60 41/60
		50	30	81	air/vapor	liver lung	angiosarcoma tumor	1/60 6/60
		0	NA	81	air only	liver lung	angiosarcoma tumor	0/150 15/150
Hamster/ Syrian Golden	M,F	10,000	30	109	air/vapor	forestomach	papilloma/ acanthoma	10/30
		6,000	30	109	air/vapor	forestomach	papilloma/ acanthoma	10/30
		2,500	30	109	air/vapor	forestomach	papilloma/ acanthoma	17/30
		500	30	109	air/vapor	forestomach	papilloma/ acanthoma	9/30
		250	30	109	air/vapor	forestomach	papilloma/ acanthoma	4/30

TABLE 5-3 (cont.)

Species/ Strain	Sex	Dose or Exposure^c (ppm)	Duration of Treatment (weeks)	Duration of Study (weeks)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
Hamster/ Syrian Golden		50	30	109	air/vapor	forestomach	papilloma/ acanthoma	3/30
		0	NA	109	air only	forestomach	papilloma/ acanthoma	3/60

QUALITY OF EVIDENCE

Strengths of Study: Chloroethene was administered by inhalation to rats, mice and hamsters at a broad range of doses. Extensive examinations of animals were performed. Duration of studies was long.

Overall Adequacy: Adequate

Comments: This report was extensive and much of the data was not reported here due to the scope of this project.

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[a] Source: Maltoni et al., 1981

[b] Purity of compound was >99.9%

[c] Exposure was for 4 hours/day, 5 days/week

NA = Not applicable

TABLE 5-4

Animal Bioassay Data for Inhalation Exposure to Chloroethene^{a,b,c}

Species/ Strain	Sex	Dose or Exposure^d (ppm)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
Rat/CD	M	50	vapor/air	liver	hemangiosarcoma	0/36
				lung	hemangiosarcoma	0/36
	F	50	vapor/air	liver	hemangiosarcoma	0/36
				lung	hemangiosarcoma	0/36
	M	250	vapor/air	liver	hemangiosarcoma	2/36
				lung	hemangiosarcoma	0/36
	F	250	vapor/air	liver	hemangiosarcoma	10/34 ($p<0.05$)^e
				lung	hemangiosarcoma	3/34
	M	1000	vapor/air	liver	hemangiosarcoma	6/34
				lung	hemangiosarcoma	4/34
	F	1000	vapor/air	liver	hemangiosarcoma	15/36 ($p<0.05$)^e
				lung	hemangiosarcoma	9/36
	M	0	air only	liver	hemangiosarcoma	0/35
				lung	hemangiosarcoma	0/35
	F	0	air only	liver	hemangiosarcoma	0/35
				lung	hemangiosarcoma	0/35

TABLE 5-4 (cont.)

Species/ Strain	Sex	Dose or Exposure^{d} (ppm)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
Mouse/CD-1	M	0	air only	respiratory tract	bronchioloalveolar adenoma	1/26
				liver	hemangiosarcoma	0/26
	F	0	air only	respiratory tract	bronchioloalveolar adenoma	0/36
				liver	hemangiosarcoma	0/36
	M	50	vapor/air	respiratory tract	bronchioloalveolar adenoma	8/29
				liver	hemangiosarcoma	3/29
	F	50	vapor/air	respiratory tract	bronchioloalveolar adenoma	4/34
				liver	hemangiosarcoma	0/34
	M	250	vapor/air	respiratory tract	bronchioloalveolar adenoma	10/29
				liver	hemangiosarcoma	7/29 ($p<0.05$)
	F	250	vapor/air	respiratory tract	bronchioloalveolar adenoma	12/34
				liver	hemangiosarcoma	16/34 ($p<0.05$)

TABLE 5-4 (cont.)

Species/ Strain	Sex	Dose or Exposure[d] (ppm)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
Mouse/CD-1	M	1000	vapor/air	respiratory tract	bronchioloalveolar adenoma	12/33
				liver	hemangiosarcoma	13/33 ($p<0.05$)
	F	1000	vapor/air	respiratory tract	bronchioloalveolar adenoma	26/36
				liver	hemangiosarcoma	18/36 ($p<0.05$)

QUALITY OF EVIDENCE

Strengths of Study:	Three different dose levels of chloroethene were tested by inhalation in two species of animals. Some statistics were reported. Chloroethene was quite pure. An extensive examination of organs and tissues was performed.
Weakness of Study:	The significance of bronchioloalveolar adenoma in mice is not reported. The duration of study was short (due to mortality).
Overall Adequacy:	Adequate

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[a] Source: Lee et al., 1978

[b] Duration of treatment and duration of study = 12 months

[c] Purity of compound = 99.8%

[d] Exposure was for 6 hours/day, 5 days/week

[e] Significantly different from controls by Fischer Exact Probability Test

TABLE 5-5

Animal Bioassay Data for Inhalation Exposure to Chloroethene[a]

Species/ Strain	Sex	Dose or Exposure[b] (ppm)	Duration of Treatment (months)	Duration of Study (months)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
Rat/CD	M,F	50	6 or 10[c]	18 or 22[c]	99.8%	air/vapor	liver	hepatocellular carcinoma	0/66
								hemangiosarcoma	0/66
							lung	bronchioloalveolar tumor	0/66
								hemangiosarcoma	0/66
		250	6 or 10[c]	18 or 22[c]	99.8%	air/vapor	liver	hepatocellular carcinoma	2/68
								hemangiosarcoma	5/68 ($p<0.05$)
							lung	bronchioloalveolar tumor	2/68
								hemangiosarcoma	2/68
		1000	6 or 10[c]	18 or 22[c]	99.8%	air/vapor	liver	hepatocellular carcinoma	7/72 ($p<0.05$)
								hemangiosarcoma	14/72 ($p<0.05$)
							lung	bronchioloalveolar tumor	4/72
								hemangiosarcoma	7/72
		0	NA	18 or 22[c]	NA	air only	lung	hemangiosarcoma hemangiosarcoma hemangiosarcoma hemangiosarcoma	1/72 0/72 0/72 0/72
Mouse/CD-1	M,F	50	1	13	99.8%	air/vapor	lung	bronchioloalveolar tumor	3/32
							liver	hemangiosarcoma	1/32
		250	1	13	99.8%	air/vapor	lung	bronchioloalveolar tumor	19/32
							liver	hemangiosarcoma	0/32
		1000	1	13	99.8%	air/vapor	lung	bronchioloalveolar tumor	20/32
							liver	hemangiosarcoma	0/32
		0	NA	13	99.8%	air only	lung	bronchioloalveolar tumor	3/32
							liver	hemangiosarcoma	0/32

TABLE 5-5 (cont.)

Species/ Strain	Sex	Dose or Exposure^b (ppm)	Duration of Treatment (months)	Duration of Study (months)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
Mouse/CD-1	M,F	50	3	15	99.8%	air/vapor	lung	bronchioloalveolar tumor	12/32
							liver	hemangiosarcoma	0/32
		250	3	15	99.8%	air/vapor	lung	bronchioloalveolar tumor	21/32
							liver	hemangiosarcoma	4/32
		1000	3	15	99.8%	air/vapor	lung	bronchioloalveolar tumor	5/20
							liver	hemangiosarcoma	16/20
		0	NA	15	NA	air only	lung	bronchioloalveolar tumor	2/32
							liver	hemangiosarcoma	0/32
		50	6	18	99.8%	air/vapor	lung	bronchioloalveolar tumor	3/16
							liver	hemangiosarcoma	1/16
		250	6	18	99.8%	air/vapor	lung	bronchioloalveolar tumor	16/20
							liver	hemangiosarcoma	9/20
		1000	6	18	99.8%	air/vapor	lung	bronchioloalveolar tumor	14/24
							liver	hemangiosarcoma	13/24
		0	NA	18	99.8%	air/vapor	lung	bronchioloalveolar tumor	11/56
							liver	hemangiosarcoma	1/56

TABLE 5-5 (cont.)

Species/ Strain	Sex	Dose or Exposure[b] (ppm)	Duration of Treatment (months)	Duration of Study (months)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)

QUALITY OF EVIDENCE

Strengths of Study:	Two animal splecies were tested. Dose and exposure levels were varied to show a dose-response. Statistics of tumor incidence with respect to dose are reported.
Weakness of Study:	The duration of treatment was too short in all cases.
Overall Adequacy:	Adequate
Comments:	This study was conducted to enhance that reported by Lee et al., 1978.

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[a] Source: Hong et al., 1981

[b] Exposure was for 6 hours/day, 5 days/week

[c] Duration of exposure was for 6 or 10 months, followed by a 12-month recovery period. The results presented are for the combined treatment-duration group.

NA - Not applicable

and 2556 mg/m³) chloroethene, 6 hours/day, 5 days/week for 1 month was sufficient to produce bronchioalveolar tumors during a 12-month latency period.

Hehir et al. (1981) conducted carcinogenicity bioassays using Fischer 344 rats and ICR or A/J mice exposed to chloroethene for single 1-hour exposures at 50, 500, 5000 or 50,000 ppm (128, 1278, 12,781 or 127,812 mg/m³), ten 1-hour exposures at 500 ppm (1278 mg/m³) or 100 1-hour exposures at 50 ppm (128 mg/m³). All animals were observed for their lifespan for gross signs of toxicity and examined histologically at the end of the study. In ICR-strain mice exposed for a single 1-hour treatment, there was a dose-related induction of pulmonary adenoma which progressed to carcinoma (Table 5-6). In A/J-strain mice exposed for ten, 1-hour exposures at 500 ppm (1278 mg/m³) and for 100 1-hour exposures at 50 ppm (128 mg/m³), lung adenomas and carcinomas occurred at increased incidences compared to controls (see Table 5-6). No carcinogenic effect was evident among Fischer F344 mice exposed to chloroethene for 1 hour at any level for 10, 1-hour periods at 500 ppm (1278 mg/m³) or for 100, 1-hour periods at 50 ppm (128 mg/m³).

A carcinogenicity study of chloroethene in rats (COBS Charles River), mice (CDI Swiss Charles River) and Syrian golden hamsters has been sponsored by the Manufacturing Chemists Association (MCA) and was reported as 8-month interim (Keplinger et al., 1975) and final results (MCA, 1980). Groups of 100 animals of each sex and species were exposed by inhalation at 0, 50, 200 or 2500 ppm (0, 128, 511 or 6391 mg/m³) chloroethene for 7 hours/day, 5 days/week. Angiosarcoma of the liver, often with metastasis to the lymph nodes or lungs, developed in a dose-related trend in all three species (Table 5-7). The development of Zymbal gland tumors and brain tumors

TABLE 5-6

Animal Bioassay Data for Inhalation Exposure to Chloroethane^{a,b}

Species/ Strain	Sex	Dose or Exposure^{c} (ppm)	Duration of Treatment	Duration of Study	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
Mouse/ICR	M,F	50,000	1 day (1 hour)	18 months	air/vapor	lung	adenoma carcinoma	45/137 3/137
		5,000	1 day (1 hour)	18 months	air/vapor	lung	adenoma carcinoma	24/143 1/143
		500	1 day (1 hour)	18 months	air/vapor	lung	adenoma carcinoma	18/139 1/139
		50	1 day (1 hour)	18 months	air/vapor	lung	adenoma carcinoma	14/139 0/139
		0	NA	18 months	air/vapor	lung	adenoma carcinoma	12/120 0/120
Rat/F344	M,F	0, 50, 500, 5000, 50,000	1 day (1 hour)	lifetime	air/vapor	lung liver	malignant	0/178-190 per dose
Mouse/A/J	M,F	500	10 1-hour exposures	20 months	air/vapor	lung	adenoma carcinoma	124/166 22/166
		0	NA	20 months	air only	lung	adenoma carcinoma	31/90 3/90
		50	100 1-hour exposures	20 months	air/vapor	lung	adenoma carcinoma	65/158 7/158
		0	NA	20 months	air only	lung	adenoma carcinoma	29/84 2/84
Rat/F344	M,F	500	10 1-hour exposures	lifetime	air/vapor	lung liver	malignant malignant	0/180 0/180
		50	100 1-hour exposures	lifetime	air/vapor	lung liver	malignant malignant	0/180 0/180
		0	NA	lifetime	air only	lung liver	malignant malignant	0/100 0/100

TABLE 5-6 (cont.)

Species/ Strain	Sex	Dose or Exposure^c (ppm)	Duration of Treatment	Duration of Study	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence

QUALITY OF EVIDENCE

Strengths of Study:	Exposures were conducted at several exposure levels using rats and mice of both sexes.
Weakness of Study:	Exposures, except for 100 1-hour treatments at 50 ppm, were very brief. Lung adenomas are usually concerned benign. The incidence of carcinomas was low and statistics were not performed. No carcinogenic affect was shown in rats.
Overall Adequacy:	Limited
Comments:	Pulmonary tumors occur spontaneously in A/J - mice and may not be a valid test for carcinogenicity.

[a] Source: Hehir et al., 1981

[b] Purity of compound not reported

NA = Not applicable

TABLE 5-7

Animal Bioassay Data for Inhalation Exposure to Chloroethene[a,b,c]

Species/ Strain	Sex	Dose or Exposure[d] (ppm)	Duration of Treatment (months)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
Rat/COBS	M,F	2500	12	air/vapor	liver	angiosarcoma	114/147
					Zymbal gland[e]	tumor	12/13
		200	12	air/vapor	liver	angiosarcoma	82/141
					Zymbal gland[e]	tumor	2/23
		50	12	air/vapor	liver	angiosarcoma	28/139
					Zymbal gland[e]	tumor	3/14
		0	12	air only	liver	angiosarcoma	0/143
					Zymbal gland[e]	tumor	0/25
Mouse/CDI Swiss	M,F	2500	9	air/vapor	liver	angiosarcoma	101/101
					lung	alveolar adenoma	101/101
						alveolar carcinoma	18/101
		200	9	air/vapor	liver	angiosarcoma	130/134
					lung	alveolar adenoma	119/134
						alveolar carcinoma	4/134
		50	9	air/vapor	liver	angiosarcoma	46/121
					lung	alveolar adenoma	92/120
						alveolar carcinoma	10/120
		0	NA	air only	liver	angiosarcoma	0/97
					lung	alveolar adenoma	10/96
						alveolar carcinoma	1/96

TABLE 5-7 (cont.)

Species/ Strain	Sex	Dose or Exposure[d] (ppm)	Duration of Treatment (months)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
Hamster/ Golden Syrian	M,F	2500	12	air/vapor	liver	angiosarcoma	56/66
		200	12	air/vapor	liver	angiosarcoma	12/88
		50	12	air/vapor	liver	angiosarcoma	7/74
		0	12	air only	liver	angiosarcoma	0/83

QUALITY OF EVIDENCE

Strengths of Study:	Three species of animals, both sexes of each were exposed at three levels. Exposure was for 12 months and a long latency was allowed. Appropriate controls were maintained. Histological examination of major organs was conducted.
Overall Adequacy:	Adequate
Comments:	Tumors were reported as total number of tumors, therefore, tumor incidence reported here (tumor bearing animals/total animals examined)

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[a] Source: MCA, 1980

[b] Duration of study was for lifetime

[c] Purity of compound was not reported

[d] Exposure was for 7 hours/day, 5 days/week

[e] Not all rats were examined for Zymbal gland tumors

NA = Not applicable

(primarily in the olfactory and frontal lobes) in rats appeared to be dose-related, but the small number of animals examined for these tumors prevents a clear conclusion. Primary lung tumors in mice, both alveolar adenoma and carcinoma, occurred with greater frequency among chloroethene-exposed groups (see Table 5-7).

The effects of inhalation exposure to chloroethene on the lungs was examined in groups of CDI Charles River male mice exposed at 2500 or 6000 ppm (6391 or 15,337 mg/m^3), 5 hours/day, 5 days/week for 5 or 6 months or at 1, 10 or 100 ppm (2.6, 26 or 256 mg/m^3) 5 hours/day, 5 days/week for 4 weeks (Suzuki, 1981, 1983). Pulmonary tumors developed in 17/17 mice exposed at 2500 ppm (6391 (mg/m^3) and 9/10 mice exposed at 6000 ppm (15,337 mg/m^3). The incidence of pulmonary tumors among mice exposed at 100, 10, 1, and 0 ppm chloroethene for 4 weeks and sacrificed at 40 weeks was 5/9, 2/9, 1/9 and 0/10, respectively. Tumors were of bronchioalveolar origin and were either tubulo-papillary or adenomatous formations. No metastases were detected.

Drew et al. (1983) tested the carcinogenic effect of chloroethene on hamsters (female Golden Syrian), rats (female F344), and mice (female Swiss CD-1 and B6C3F$_1$) exposed by inhalation at 200, 100, and 50 ppm (511, 256 or 128 mg/m^3), respectively (6 hours/day, 5 days/week). Exposure durations of 6, 12, 18 or 24 months in young animals or 6 and 12 months in aged animals (held for 6-18 months before exposure) were used to test the effect of exposure duration and animal age on cancer induction. In rats exposed early in life for 6, 12, 18 or 24 months an increased incidence ($p<0.01$) of liver hemangiosarcomas hepatocellular carcinoma and mammary gland fibroadenoma was reported compared to controls (Table 5-8). In rats exposed for 6 months during the period 6-12 months of the study, a similar tumor

TABLE 5-8

Animal Bioassay Data for Inhalation Exposure to Chloroethene[a,b]

Species/ Strain	Sex	Dose or Exposure[c] (ppm)	Duration of Treatment (months)	Duration of Study (months)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
Rat/F344	F	100	6	24	air/vapor	liver	hemangiosarcoma	4/76[d]
							hepatocellular carcinoma	3/75
						mammary gland	fibroadenoma	28/76[d]
		100	12	24	air/vapor	liver	hemangiosarcoma	11/55[d]
							hepatocellular carcinoma	4/56[d]
						mammary gland	fibroadenoma	28/56[d]
		100	18	24	air/vapor	liver	hemangiosarcoma	13/55[d]
							hepatocellular carcinoma	8/54[d]
						mammary gland	fibroadenoma	24/55[d]
		100	24	24	air vapor	liver	hemangiosarcoma	19/55[d]
							hepatocellular carcinoma	9/55[d]
						mammary gland	fibroadenoma	26/55[d]
		0	NA	24	air only	liver	hemangiosarcoma	1/112
							hepatocellular carcinoma	1/112
						mammary gland	fibroadenoma	24/112
Hamster/ Golden Syrian	F	200	6	24	air/vapor	all sites	hemangiosarcoma	13/88[d]
						mammary gland	carcinoma	28/87[d]
						stomach	adenoma	23/88[d]
		200	12	24	air/vapor	all sites	hemangiosarcoma	4/52[d]
						mammary gland	carcinoma	31/52[d]
						stomach	adenoma	3/50[e]
		200	18	24	air/vapor	all sites	hemangiosarcoma	2/103
						mammary gland	carcinoma	47/102[d]
						stomach	adenoma	20/101[d]
		0	NA	24	air only	all sites	hemangiosarcoma	0/143
						mammary gland	carcinoma	0/143
						stomach	adenoma	5/138

TABLE 5-8 (cont.)

Species/ Strain	Sex	Dose or Exposure^c (ppm)	Duration of Treatment (months)	Duration of Study (months)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
Mouse/ B6C3F1	F	50	6	18	air/vapor	all sites	hemangiosarcoma	46/67^d
						mammary gland	carcinoma	29/67^d
		50	12	18	air/vapor	all sites	hemangiosarcoma	69/90^d
						mammary gland	carcinoma	37/90^d
Mouse/ B6C3F1	F	0	NA	24	air only	all sites	hemangiosarcoma	4/69
						mammary gland	carcinoma	3/69
Mouse/ Swiss	F	50	6	18	air/vapor	all sites	hemangiosarcoma	29/67^d
						mammary gland	carcinoma	33/67^d
						lung	carcinoma	18/65^d
		50	12	18	air/vapor	all sites	hemangiosarcoma	30/47^d
						mammary gland	carcinoma	22/47^d
						lung	carcinoma	15/47^d
		0	NA	18	air only	all sites	hemangiosarcoma	1/71^d
						mammary gland	carcinoma	2/71^d
						lung	carcinoma	9/71^d

QUALITY OF EVIDENCE

Strengths of Study: The chloroethene was administered at a maximum tolerated dose. Several species of rodents were tested. Complete histopathological examinations were performed. Statistics were performed.

Weakness of Study: Only female animals were tested.

Overall Adequacy: Adequate

Comments: Additional tests by these authors showed little or no carcinogenic effect in rats and hamsters if chloroethene exposure was started after 12 months of non-exposure.

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[a] Source: Drew et al., 1983

[b] Purity of compound not reported

[c] Exposure was for 6 hours/day, 5 days/week

[d] $p<0.01$ (life table analysis)

[e] $p<0.05$ (life table analysis)

NA = Not applicable

response occurred. In rats exposed for 6 months during the interval 12-18 months or 18-24 months, no carcinogenic effect was evident. Rats exposed for 12 months during months 0-12 developed increased incidences of liver and mammary tumors while those treated during months 12-24 showed no carcinogenic effect. In hamsters, hemangiosarcomas, mammary gland carcinomas and stomach adenomas were increased among animals treated early in their lifetime (see Table 5-8). Hamsters treated for 6 or 12 months during the interval 12-24 months showed little evidence of a carcinogenic effect. In mice, hemangiosarcoma, primarily of the peritoneum or dermis, and mammary gland carcinoma developed in both strains during all treatment intervals and durations, but the highest incidences occurred when treatment was during the initial 12 months of the study (see Table 5-8). Swiss mice also developed an increased incidence of lung carcinoma following chloroethene inhalation exposure. This study (Drew et al., 1983) provides strong evidence that exposure to chloroethene early in life leads to a greater carcinogenic risk.

Maltoni et al. (1983) and Cotti et al. (1983) treated rats with chloroethene by inhalation at 2500 ppm (6391 mg/m^3) 4-7 hours/day, 5 days/week from day 12 of gestation and after birth until offspring were 1 year of age. Liver angiosarcoma developed in 32/56 males and 38/55 females, having an average latency period of ~50 weeks. Lung metastases occurred in ~40% of the rats with liver angiosarcoma. Brain tumors (medulloepithelioma, medulloblastoma and neuroblastoma) developed in 27/57 males and 28/57 females with an average latency of ~48 weeks.

An oral carcinogenicity study of chloroethene was conducted by Feron et al. (1981) using male and female Wistar rats (n=60-80/sex). Chloroethene exposure resulted from the addition of PVC powder with a high chloroethene content in the diet or by gastric intubation of chloroethene in soybean oil. Doses from PVC-containing diets were 0, 1.8, 5.6, and 17.0 mg chloroethene/kg/day; intubation at 300 mg/kg/day was given on 5 days/week. Rats were treated for their lifetime. Mortality of rats treated at 300 mg/kg/day reached ~40% by 18 months; most rats that died had severe lesions of the lungs and liver, so that treatment was discontinued at 84 weeks. A dose-related increase in nonneoplastic hepatic lesions and neoplastic changes in the liver and lungs were reported (Table 5-9). These data suggest that hepatic angiosarcomas develop at high dose levels while hepatocellular carcinoma occurs at doses as low as 1.8 mg/kg/day.

The Dow Chemical Company (1984) conducted a long-term carcinogenicity study of chloroethene administered as PVC in the diet of Wistar rats. Dietary levels were established to give doses of 0.0, 0.014, 0.13 and 1.3 mg chloroethene/kg bw/day and were administered for up to 149 weeks (lifespan). The high-dose group consisted of 50 rats of each sex while all other groups contained 100 animals of each sex. Additional groups of 10 animals of each sex were maintained on the treated diets for interim sacrifices at 9 and 18 months. General health, body weights and food consumption were not affected by chloroethene treatment while mortality in the high-dose group was slightly increased. Clinical chemistry parameters were not affected. Histopathological examination of the liver showed an increased incidence of liver nodules and preneoplastic foci among males and females ingesting 1.3 mg chloroethene/kg/day and among female rats treated at 0.13 and 0.014 mg/kg/day (Section 5.5.). Female rats exposed at 1.3 mg/kg/day had an increased incidence (9/49) of hepatic neoplastic nodule compared to controls (0/98). No other carcinogenic effects were reported.

TABLE 5-9

Bioassay Data for Wistar Rats Exposed to Chloroethene^{a,b,c}

Exposure Route	Sex	Dose or Exposure^{d} (mg/kg/day)	Duration of Treatment (weeks)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
Oral (gavage)	F	300^{d}	84	soybean oil	liver	neoplastic nodule	2/54
						hepatocellular carcinoma	0/54
						angiosarcoma	29/54
					lung	angiosarcoma	23/54
Oral (diet)	F	17.0	143	PVC	liver	neoplastic nodule	44/57 ($p<0.001$)^{e}
						hepatocellular carcinoma	29/57 ($p<0.001$)^{e}
						angiosarcoma	9/57 ($p<0.001$)^{e}
					lung	angiosarcoma	5/57 ($p<0.05$)^{e}
		5.6	143	PVC	liver	neoplastic nodule	39/59 ($p<0.001$)^{e}
						hepatocellular carcinoma	19/59 ($p<0.001$)^{e}
						angiosarcoma	2/59
					lung	angiosarcoma	3/59
		1.8	143	PVC	liver	neoplastic nodule	26/58 ($p<0.01$)^{e}
						hepatocellular carcinoma	4/58
						angiosarcoma	0/58
					lung	angiosarcoma	0/58
		0.0	NA	untreated diet only	liver	neoplastic nodule	2/57
						hepatocellular carcinoma	2/57
						angiosarcoma	0/57
					lung	angiosarcoma	0/57
Oral (gavage)	M	300^{d}	84	soybean oil	liver	neoplastic nodule	3/55
						hepatocellular carcinoma	1/55
						angiosarcoma	27/57
					lung	angiosarcoma	19/55
Oral (diet)	M	17.0	143	PVC	liver	neoplastic nodule	23/59 ($p<0.001$)^{e}
						hepatocellular carcinoma	8/59 ($p<0.001$)^{e}
						angiosarcoma	27/59 ($p<0.001$)^{e}
					lung	angiosarcoma	19/59 ($p<0.01$)^{e}

TABLE 5-9 (cont.)

Exposure Route	Sex	Dose or Exposure[d] (mg/kg/day)	Duration of Treatment (weeks)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
Oral (diet) (cont.)	M	5.6	143	PVC	liver	neoplastic nodule	7/56 ($p<0.01$)[e]
						hepatocellular carcinoma	2/56 ($p<0.01$)[e]
						angiosarcoma	6/56 ($p<0.05$)[e]
					lung	angiosarcoma	7/56
		1.8	143	PVC	liver	neoplastic nodule	1/58
						hepatocellular carcinoma	1/58
						angiosarcoma	0/58
					lung	angiosarcoma	0/58
		0.0	NA	untreated diet only	liver	neoplastic nodule	0/55
						hepatocellular carcinoma	0/55
						angiosarcoma	0/55
					lung	angiosarcoma	0/55

QUALITY OF EVIDENCE

Strengths of Study: The dose of chloroethene was determined following gastrointestinal digestion of PVC- containing diet. Treatment was for the lifetime of the rats. Several dose levels were administered. A large number of rats of both sexes were used in each group.

Weakness of Study: No control group for rats treated by gavage was included

Overall Adequacy: Adequate

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[a] Source: Feron et al., 1981

[b] Duration of study was 143 weeks

[c] Purity of compound was not reported

[d] Dosage given 5 days/week

[e] Compared with controls using chi-square

NA = Not applicable

Maltoni et al. (1980, 1981) and Rice (1981) reported that rats exposed in utero to chloroethene on days 12-18 of development had an increased incidence of Zymbal gland carcinoma, nephroblastoma and subcutaneous angiosarcoma than expected. Pregnant Sprague-Dawley rats (n=19) were exposed at 6000 and 10,000 ppm (15,337 and 25,562 mg/m^3) for 4 hours/day on days 12-18 of gestation and the progeny were observed for 115 weeks. A total of 86 progeny resulted, 54 exposed at 10,000 ppm and 32 at 6000 ppm. Three Zymbal gland carcinomas, 1 nephroblastoma and 2 angiosarcomas occurred among the high-dose progeny, while 1 Zymbal gland carcinoma and 2 angiosarcomas developed among the low dose rats.

In humans, the carcinogenicity of chloroethene has been demonstrated in several reports, causing angiosarcoma of the liver and some evidence of increased brain, lung and circulatory system cancers among occupationally exposed workers. According to the International Agency for Research on Cancer (IARC, 1982) the epidemiological data provide "sufficient" evidence to classify chloroethene as a Group 1 (human carcinogen) chemical. Reviews of the epidemiological evidence on chloroethene have been conducted by IARC (1979), Wagoner et al. (1980), U.S. EPA (1980, 1983a), Tamburro (1984) and Kalmaz and Kalmaz (1984). Due to the number of epidemiological reports summarized in these reviews and the number of case reports (Creech and Johnson, 1974; Evans et al. 1983; Dow Chemical Company, 1983) of angiosarcoma and carcinoma of the liver, this document presents select data which provide sufficient data for the assessment of human cancer risk.

In a retrospective study of 161 deaths among chloroethene workers, Monson et al. (1974) reported 8 cases of hepatic and biliary cancer (8 angiosarcomas) while only 0.7 were expected (relative risk = 11.4) (Table 5-10). In addition, 5 cases of brain cancer, 13 cases of lung cancer, 13 digestive tract cancers and 5 hematopoietic system cancers were identified,

TABLE 5-10

Bioassay Data for Humans Occupationally Exposed to Chloroethene[a],[b]

Size of Exposed Population	Size of Control Population	Sex	Target Organ	Tumor Type	Number of Cases Observed	Number of Cases Expected	Relative Risk
161	161	M	liver and biliary tract	cancer	8	0.7	11.4
			brain	cancer	5	1.2	4.2
			lung	cancer	13	7.9	1.6
			digestive	cancer	13	8.3	1.6
			lymphatic and hematopoietic system	cancer	5	3.4	1.5

QUALITY OF EVIDENCE

Strengths of Study: Deaths in a chloroethene-exposed population were compared with a comparable age/time/cause-specific reference population. The incidence of several causes of death were examined.

Weakness of Study: The levels of exposure and duration of exposure are not reported. No statistics are reported.

Overall Adequacy: Adequate

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[a] Source: Monson et al., 1974

[b] Level and duration of exposure not reported

NR = Not reported

all representing risk ratios greater than expected and resulting in a 50% excess of death due to all types of cancer. Waxweiler et al. (1976) reported 7 cases of biliary and liver cancer, 3 brain or CNS cancers, 3 hematopoietic cancers and 11 respiratory tract cancers among 131 deaths in a group of 1287 chloroethene workers. Workers were exposed for at least 5 years and a 15 year latency was allowed. Based on the expected number of cases from United States mortality rates all four cancer types occurred more frequently among the chloroethene-exposed workers (Table 5-11). Statistically significant increases occurred for liver and biliary cancer ($p<0.01$), brain cancers ($p<0.05$) and respiratory tract cancers ($p<0.05$).

Among a group of 750 Swedish chloroethene and PVC-production workers, Byren et al. (1976) reported 4 cases of liver/pancreatic cancer, 2 of which were confirmed hepatic angiosarcomas among a subgroup exposed for >10 years. Based on Swedish mortality records only 0.68 cases were expected ($p=0.005$) (Table 5-12). In addition, another case of liver hemangiosarcoma was diagnosed after the data were compiled. The two cases of brain cancer also represented a statistically significant ($p<0.05$) increase compared to the expected number of cases (0.33). Lung cancer deaths were slightly increased compared to expected (3 cases vs. 1.78 expected) but was not statistically significant.

Fox and Collier (1977) conducted a mortality analysis of 7409 workers from eight factories involved in the production of PVC. A majority of the study cohort was employed for <10 years at the time of the study so that the latency period was relatively short and minimized representation of cancer risk (Infante,, 1981). A total of 4 liver cancer deaths were observed (1.64 expected; Table 5-13), while 3 of the cases occurred among workers of a factory in operation since 1944 (longest latent period). The expected number of liver cancer deaths among this factory subgroup was 0.13 ($p<0.01$).

TABLE 5-11

Bioassay Data for Humans Occupationally Exposed to Chloroethene[a,b]

Size of Exposed Population	Size of Control Population	Sex	Duration of Exposure	Target Organ	Tumor Type	Number of Cases Observed[d]	Number of Cases Expected	Relative Risk (p value)
1287	U.S. death rates	M,F	≥5 years	liver and biliary tract	cancer	7	0.4	17.5 ($p<0.01$)
				brain and CNS	cancer	3	0.6	5.0 ($p<0.05$)
				lymphatic and hematopoietic	cancer	3	1.7	1.8 (NS)
				respiratory system	cancer	11	5.7	1.9 ($p<0.05$)

QUALITY OF EVIDENCE

Strengths of Study: Tumor incidences were analyzed on the basis of latency period. Statistical analyses of different types of cancer compared to expected values were performed. The study was of workers with ≥5 years exposure.

Weakness of Study: Levels of exposure were not available.

Overall Adequacy: Adequate

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[a] Source: Waxweiler et al., 1976

[b] Level of exposure not reported

[c] Incidence of tumors after 15-year latency

NS = Not significant

TABLE 5-12

Bioassay Data for Humans Occupationally Exposed to Chloroethene*

Size of Exposed Population	Size of Control Population	Sex	Level of Exposure	Duration of Exposure	Target Organ	Tumor Type	Number of Cases Observed	Number of Cases Expected	Relative Risk (p value)
750	1969 Swedish population	M	periodically up to 15,000 ppm	>10 years	liver/ pancreas	cancer	4	0.68	5.8 (p=0.005)
				<1 to >10 years	brain	cancer	2	0.33	6.1 (p=0.043)
				<1 to >10 years	lung	cancer	3	1.78	1.7 (p=0.26)

QUALITY OF EVIDENCE

Strengths of Study:	The exposed population was compared to the Swedish population. The incidence of liver tumors was reported based on lengths of exposure. Statistics were compiled to show significant increases in tumor incidences.
Weakness of Study:	Specific levels of exposure are not reported. A relatively small number of cancer deaths was examined.
Overall Adequacy:	Adequate

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*Source: Byren et al., 1976

TABLE 5-13

Bioassay Data for Humans Occupationally Exposed to Chloroethene*

Size of Exposed Population	Size of Control Population	Sex	Level of Exposure (ppm)	Duration of Exposure	Target Organ	Tumor Type	Number of Cases Observed	Number of Cases Expected	Relative Risk
7409	death rates for England and Wales	M	<25 to >200	6-20 years	liver	cancer	4	1.64	2.44

QUALITY OF EVIDENCE

Strengths of Study: Levels of exposure of workers were estimated from air-sample metering. Duration of exposure was reported. The exposed population was compared to death rates (based on age groups) of England and Wales.

Weakness of Study: Few deaths were reported. No statistics were reported.

Overall Adequacy: Limited

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*Source: Fox and Collier, 1977

Nakamura (1983) conducted a retrospective mortality study of Japanese workers from 25 plants producing chloroethene and/or PVC between 1950-1975. A group of 4524 males having at least 1 year exposure before December 31, 1964 were identified. A total of 209 deaths were confirmed and all death certificates obtained while the fate of 29 workers was unknown. The cohort was separated into "PVC workers" and "other workers". Among the PVC workers the number of deaths due to malignant neoplasms was significantly increased (37 observed vs 26.9 expected; $p<0.05$). Deaths due to liver cancer were also significantly increased (6 cases vs 2.54 expected; $p<0.05$) while deaths due to other cancers were not significantly different from expected (Table 5-14). There was no increase in deaths due to cancer in general or specific sites among the "other workers" group.

A retrospective mortality study of 454 male workers exposed to chloroethene during its production and polymerization to PVC was conducted by Heldaas et al. (1984). The cohort consisted of men working for at least 1 year during 1950-1969 and the group was followed during 1953-1979. A total of 23 cancer deaths were observed (20.2 expected) with 1 case of liver angiosarcoma, 5 lung cancers (2.8 expected), 3 colon cancers (1.4 expected), 2 thyroid cancers (0.16 expected) and 4 malignant melanomas of the skin (0.8 expected) (Table 5-15). In addition, two cases of malignant melanoma were diagnosed after the termination date and were not included. The authors (Heldaas et al., 1984) noted that "the increased incidence of cancer is accounted for almost entirely by the high exposure group" when workers were grouped by exposure depending on job classification. The authors also noted that this study is consistent with others in that it shows an increased risk of cancer at several sites among chloroethene exposed workers. The high level of malignant melanoma among this group of workers is unique and warrants further attention.

TABLE 5-14

Bioassay Data for Humans Occupationally Exposed to Chloroethene[a,b]

Size of Exposed Population	Size of Control Population	Sex	Duration of Exposure	Target Organ	Tumor Type	Number of Cases Observed	Number of Cases Expected	Relative Risk (p value)
4524	Japanese mortality rates	M	>1 year	all sites	malignant neoplasm	37	26.94	1.37 ($p<0.05$)
				liver	cancer	6	2.54	2.36 ($p<0.05$)

QUALITY OF EVIDENCE

Strengths of Study: A large group of workers having at least 1 year of exposure and 10 years latency was studied. Death certificates were obtained for a majority of deceased employees.

Weakness of Study: Exposure levels were not determined. Limited data on diagnosis and cause of death available from death certificates prevented specific classification of cancer types.

Overall Adequacy: Adequate

Comments: Data were for PVC-workers. Non PVC-workers showed no increase in cancer deaths.

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[a] Source: Nakamara, 1983

[b] Level of exposure not significant

TABLE 5-15

Bioassay Data for Humans Occupationally Exposed to Chloroethene[a]

Size of Exposed Population	Size of Control Population	Sex	Level of Exposure	Duration of Exposure	Target Organ	Tumor Type	Number of Cases Observed	Number of Cases Expected	Relative Risk
454	Norway Cancer Mortality Records	M	varies over years[b]	>1 year	all sites	cancer	23	20.2	1.1
					liver	angiosarcoma	1	NR	NA
					lung	cancer	5	2.8	1.8
					colon	cancer	3	1.4	2.1
					thyroid	cancer	2	0.16	12.5
					skin	melanoma	4	0.8	5.0

QUALITY OF EVIDENCE

Strengths of Study: The cohort consisted of workers exposed for at least 1 year having a minimum of 10 years latency. Exposure levels were estimated.

Weakness of Study: The small number of cancer deaths prevents a definitive conclusion.

Overall Adequacy: Adequate

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[a] Source: Heldaas et al., 1984

[b] Estimated 2000 ppm in 1950-1954; 1000 ppm in 1955-1959; 500 ppm in 1960-1967; 100 ppm in 1968-1974

NA = Not applicable; NR = Not reported

In a brief review of cases of liver angiosarcoma among chloroethene-exposed workers, Spirtas et al. (1983) identified 95 total cases between 1955-1981. The average latency period was about 20 years so that all cancer cases as a result of exposure have not yet occurred.

5.2. MUTAGENICITY

The mutagenicity of chloroethene has been reviewed by IARC (1979, 1982), U.S. EPA (1980, 1984a,b), Fabricant and Legator (1981) and Duverger et al. (1981). A summary of representative mutagenicity data on chloroethene is presented in Table 5-16.

In the reverse mutation assay in Salmonella typhimurium, chloroethene vapors have been positive in the presence of hepatic activation systems from rats, mice and human biopsy specimens (Bartsch et al., 1975). In the absence of metabolic activation, chloroethene was not mutagenic or slightly positive, while activation greatly enhanced the mutagenic response. Metabolites of chloroethene, chloroacetaldehyde, chloroethanol and chloroethylene oxide were also mutagenic (Malaveille et al., 1975). The mutagenic activity of chloroethene appears to be dependent on its oxidation to reactive metabolites (Garro et al., 1976; Greim et al., 1977). Chloroethene appears to be more effective in inducing mutations in base-pair sensitive strains of S. typhimurium (TA1530, TA1535, TA100 and G-46). In liquid medium or plate incorporation assays using aqueous or methanolic chloroethene with rat liver activation system, no mutagenic effect occurred in S. typhimurium TA1535 (Rannug et al., 1974; DeMeester et al., 1980), TA1530 (Poncelet et al., 1980) TA100 (Elmore et al., 1976) and G-46 (Bartsch et al., 1975, 1979). Using DNA repair-deficient strains of Bacillus subtilis, Elmore et al. (1976) reported no growth inhibition by chloroethene (at 0.0106M) in the

TABLE 5-16

Summary of Mutagenicity Data on Chloroethene

Assay	Indicator/ Organism	Compound and/or Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	*Salmonella typhimurium*	very high	vapor	11%x75 minutes	+/-	+	No mutagenic activity without metabolic activation; NADP necessary; tested in TA1535	Rannug et al., 1974
		very high	liquid medium	NR	+	-	Negative in TA1535	Rannug et al., 1974
		very high	vapor	20% for 90 minutes	+	-	Negative in TA1536, TA1537, TA1538 (frameshift)	Rannug et al., 1974
		99.9%	vapor	0, 0.2, 2.0, 20% in air	+/-	+	Mutagenic in TA1530, TA1535, G-46 with or without metabolic activation from rat, mouse or human liver	Bartsch et al., 1975, 1979; Bartsch and Montesano, 1980
		99.9%	liquid medium	0.083 M	+	-	No mutagenic effect in TA1530, TA1535 or G-46	Bartsch et al., 1975, 1979
		NR	vapor	0, 0.4, 1.2, 4.8, 9.4, 115.4% in air	+/-	+	Tested in strain TA1535 for base-pair substitutions	Andrews et al., 1976
		NR	liquid medium	0.0105 M	-	-	Chloroethene was negative in TA100 while several metabolites were positive	Elmore et al., 1976
		NR	vapor	20% vapor	+/-	+	Positive in TA100	Simmon, 1978
		>99.9%	plate incorporation	NR	+	-	Tested in strain TA1530	Poncelet et al., 1980
		>99.9%	liquid medium	NR	+	-	Tested in strain TA1530	Poncelet et al., 1980
		>99.9%	vapor	2%x16 hours	+/-	+	Positive in strain TA1530 with and without metabolic activation	Poncelet et al., 1980; DeMeester et al., 1980

TABLE 5-16 (cont.)

Assay	Indicator/ Organism	Compound and/or Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Rec-repair	*Bacillus subtilis*	NR	plate-disc	0.0106 M	-	-	No growth inhibition with repair-deficient strains 168M, Her-9, FB-13, MC-1. Metabolites of chloroethene were mutagenic	Elmore et al., 1976
Forward mutation	*Escherichia coli*	>99.9%	liquid medium	10.6 mM	+/-	+	Strain K-12, metabolic activation necessary; MTR resistance	Greim et al., 1975
Reverse mutation	*E. coli*	>99.9%	liquid medium	10.6 mM	+/-	+	Strain K-12 for gal^+, arg^+, nad^+	Greim et al., 1975
Reverse mutation	*Saccharomyces cerevisiae*	NR	liquid medium	0.275 and 0.55%	-	-	No mutagenic effect in strain D5	Shahin, 1976
Forward mutation	*Schizo-saccharomyces pombe*	99.99%	liquid medium	16, 32, 48 mM	+/-	+	Mutagenic only with metabolic activation; metabolites active with or without activation	Loprieno, 1977
Forward mutation	*Neurospora crassa*	99.9%	vapor and ethanol solution	25 and 50%	+/-	-	Conidia were exposed for 3.5 or 24 hours: strain nic-1	Drozdowicz and Huang, 1977
Recessive lethal	*Drosophila melanogaster*	>99.99%	vapor	30-50,000 ppm x2-17 days	NA	+	Increased recessive-lethals after 850 ppm for 2 days or 30 ppm for 17 days	Verburgt and Vogel, 1977
Recessive lethal	*D. melanogaster*	99.995%	vapor	1-20% in air for 3 hours	NA	+	Increased recessive lethal mutations following treatment at all levels	Magnusson and Ramel, 1978
HGPRT	CHO	NR	vapor	NR	+/-	+	Mutagenic only with metabolic activation	Krahn, 1979; Krahn et al., 1982
Cell transformation	neonatal hamster kidney cells	NR	liquid medium	0.025-250 μg/mℓ	+	-	No increase in transformed cells	Styles, 1977
Cell transformation	neonatal hamster kidney cells	NR	vapor	10-50%	+	+	5-fold increase in transformed cells	Styles, 1977
Forward mutation	Chinese hamster cells - V79	99.9%	vapor	5-30%	+	+	8-azaguenine and ouabain resistance induced	Drevon and Kuroki, 1979

TABLE 5-16 (cont.)

Assay	Indicator/ Organism	Compound and/or Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Dominant lethal	Male CD-1 mice	NR	inhalation	3000-30,000 ppm 6 hours/day x 5 days	NA	-	No increase in the number of post-implantational fetal deaths	Anderson et al., 1977
Dominant lethal	Male CD-1 mice	NR	inhalation	10,000 ppm 4 hours/day for 5 days or 5000 ppm 4 hours/day 5 days/week x 10 weeks	NA	-	No evidence of dominant lethal mutations	Himeno et al., 1983
Micronucleus test	CBA male mouse	NR	inhalation	5% for 4 hours	NA	+	Increased frequency of polychromatic micronucleated cells	Jenssen and Ramel, 1980
Micronucleus test	C57B1/65 mouse erythrocytes	NR	inhalation	50,000 ppm for 6 hours	NA	+	Polychromatic micronucleated erythocytes increased 10- to 20-fold	Richardson et al., 1983
Chromosome damage	Wistar male rats Bone marrow cell	NR	inhalation	1500 ppm 6 hours/day 5 days/week for 3 months	NA	+	Increased chromatid gaps	Anderson and Richardson, 1981
Chromosome damage	Chinese hamster (M,F) bone marrow cells	NR	inhalation	1.25-5% for 6, 12 or 24 hours	NA	+	Dose-related increase in sister chromatid exchanges and chromosome aberrations	Basler and Roehrborn, 1980
Forward mutation	Mice (C57B1/65 x Han)	NR	inhalation	4600 ppm x 6 hours on 12th day of gestation	NA	-	No increase in altered pigment spots on progeny. No increase in somatic gene mutations	Peter and Ungvary, 1980
Chromosomal aberrations	Human (n-30) lymphocytes	NR	vapor-occupational	5000 ppm	NA	+	Increased gaps and iso-gaps in 200 metaphases from lymphocytes of exposed workers	Fleig and Thiess, 1978
Chromosomal aberrations	Human lymphocytes	NR	vapor-occupational	0-6000 ppm for 10-27 years	NA	+	Increased chromosomal aberrations and sister chromatid exchanges	Kucerova et al., 1979
Chromosomal aberrations	Human lymphocytes	NR	vapor-occupational	1-2000 ppm	NA	+	Increased chromosome breaks and sister chromatid exchanges	Hansteen et al., 1978

NA = Not applicable; NR = not reported

absence of metabolic activation (see Table 5-16). Metabolites of chloroethene, chloroethylene oxide and chloroacetaldehyde, were very active in the absence of metabolic activation. Greim et al. (1975) reported that chloroethene was positive in a forward mutation assay (resistance to 5-methyl-DL-tryptophane) and in reverse mutation systems (gal$^+$, arg$^+$, nad$^+$) using Escherichia coli strain K-12 only when a metabolic activation system was provided. In the yeasts, Schizosaccharomyces pombe and Saccharomyces cerevisiae, forward mutations and mitotic gene conversions, respectively, were induced by chloroethene exposure only when a metabolic activation system was provided (Loprieno, 1977). In a mutagenicity assay for forward mutations in Neurospora crasso, exposure to chloroethene by vapor or in ethanolic liquid medium was not positive with or without metabolic activation (Drozdowicz and Huong, 1977).

Chloroethene vapors caused an increased frequency of recessive lethal mutations in Drosophila melanogaster, but no increase in dominant lethal mutations, translocations or sex-chromosome loss (Verburgt and Vogel, 1977; Magnusson and Ramel, 1978). Chloroethene vapors were mutagenic and effective in transforming mammalian cells in vitro with metabolic activation (Krahn, 1979; Krahn et al., 1982; Sytles, 1977; Drevon and Kuroki, 1979). In liquid medium, however, chloroethene did not increase the transformation of neonatal hamster kidney cells in culture (Styles, 1977).

The dominant-lethal assay using male CD-1 mice has been used to test the mutagenic potential of chloroethene in vivo. Two studies (Anderson et al., 1977; Himeno et al., 1983) have reported no increase in post-implantational fetal deaths after adult male mice were exposed by inhalation prior to mating (see Table 5-16). In the in vivo exposure assay for micronuclei in erythrocytes, two studies (Jenssen and Ramel, 1980; Richardson et al., 1983) have reported positive effects in mice exposed by inhalation at 50,000 ppm (127,812 mg/m³) for 4-6 hours. An increase in chromosomal and chromatid damage in bone marrow cells has been reported in male rats (Anderson and Richardson, 1981) and Chinese hamsters (Basler and Roehrborn, 1980) exposed to chloroethene by inhalation.

Evidence of mutagenicity in humans occupationally exposed to chloroethene has been reviewed by Hopkins (1980). A number of the available studies reported that chloroethene caused lymphocyte chromosomal aberrations among exposed workers; Fleig and Thiess, 1978; Kucerova et al., 1979; Hansteen et al., 1978) (see Table 5-16). Although some of the positive studies are limited by small sample sizes, taken collectively they support the conclusion that chloroethene is mutagenic to humans following occupational exposure.

5.3. TERATOGENICITY

The effects of chloroethene on embryonal and fetal development following maternal inhalation were determined by John et al. (1977, 1981). Groups of 30-40 female CF-1 mice were exposed to 0, 50 and 500 ppm (0, 128 and 1278 mg/m³), 7 hours/day on days 6-15 of gestation. Pregnant Sprague-Dawley rats (n=20-35/group) and New Zealand rabbits (n=15-20/group) were exposed at 0, 500 and 2500 ppm (0, 1278 and 6391 mg/m³) chloroethene for 7 hours/day on days 6-15 (rats) or 6-18 of gestation (rabbits). Females were observed for signs of maternal toxicity and body weights monitored during the study. Animals were sacrificed on days 18 (mice), 21 (rats) or 29 (rabbits) of gestation and uteri examined for live, dead and resorbed fetuses. Fetuses were weighed, measured and examined for external, internal and skeletal anomalies. Female mice exposed at 500 ppm had decreased weight gain and food consumption; mortality was 5/29. No toxic effects were observed in the rat or rabbit dams. Among mice exposed at 500 ppm (1278 mg/m^3), fetal resorptions were increased, litter size was decreased and fetal body weights were reduced. Fetal crown-rump length was greater among mice exposed at 50 ppm (128 mg/m^3) than among controls. In rats, one death (1/17) occurred among dams exposed at 2500 ppm (6391 mg/m^3). There was no effect on litter size, implantations or resorptions among rats exposed at either level. Fetal body weight was decreased among rats exposed at 500 ppm but not among those exposed at 2500 ppm. In rabbits a decreased number of live fetuses/litter was observed among those exposed at 500 ppm but not among the 2500 ppm exposure group. No effects on fetal body weight or length among exposed rabbits was observed. Examination for anomalies revealed only delayed ossification of the skull among mice exposed at 500 ppm with no increase in skeletal or soft tissue anomalies among fetuses of either dose group. Similarly, in rats there was no increase in skeletal or soft tissue anomalies, but delayed ossification of the skull was evident among fetuses exposed at 2500 ppm. Among rabbits, no treatment-related anomalies were observed. Delayed ossification of sternebrae occurred more frequently among fetuses exposed at 500 ppm compared to controls, but this trend was not evident among fetuses exposed at 2500 ppm.

The teratogenicity and embryotoxic effects of chloroethene vapor were determined in CFY rats exposed on days 1-9, 8-14, or 14-21 of gestation (Ungvary et al., 1978). Exposure was at 1565 ppm (4000 mg/m^3) continuously during the treatment period. The group exposed to chloroethene during days 1-9 of gestation was also given physiological saline by subcutaneous injection on days 7 and 8 as part of another test. On the 21st day of gestation dams were sacrificed and uteri examined for live, dead and resorbed fetuses. Increased fetal loss ($p<0.05$) was reported among the 19 litters exposed on days 1-9 of gestation. There was a tendency for increased fetal loss and resorption among rats exposed on days 8-14 but no similar effect among fetuses exposed during the last week of development. Based on a gross and internal examination (about half of the live fetuses were dissected) there was no increase in gross, internal or skeletal malformations among any group of chloroethene-exposed fetuses. These data demonstrate maternal toxicity and embryotoxic effects occurring concomitantly when exposure was during early gestation, but no evidence of a teratogenic effect was demonstrated (Ungvary et al., 1978).

In a Bulgarian study available as an English abstract (Mirkova et al., 1978), continuous inhalation exposure to chloroethene at 2.4 ppm (6.15 mg/m^3) in rats for 21 days of pregnancy resulted in early postimplantational resorptions. Delayed skeletal ossification, decreased fetal weight, frequent hematomas, hydrocephaly (54.4% of fetuses) and encephalocoele (2.53% of fetuses) were also reported. Among neonates, signs of toxic hepatopathy were reported. In a Russian study available as an English abstract (Sal'nikova and Kitsovskaya, 1980), rats were exposed to chloroethene at 1.9 ppm (4.8 mg/m^3) or 14 ppm (35.5 mg/m^3) for 4 hours/day during the entire gestational period. Hemorrhages occurred among 49 and 51% of the fetuses exposed at the two dose levels and organ weight changes and hematological changes were reported. No malformations were reported.

A study conducted by the National Institute for Occupational Safety and Health examined the rate of fetal loss and other health effects among workers exposed to chloroethene during the production of PVC (Waxweiler et al., 1977). The results of a questionnaire as to outcomes of pregnancies were analyzed by age of father at the time of conception, and before or after exposure at the plant. A total of 148 pregnancies occurred prior to exposure and 139 occurred after exposure to chloroethene. In comparison 159 and 273 pregnancies occurred among the reference control group (rubber workers not exposed to chloroethene) before and after their employment. The percent of fetal loss was 6.1 and 6.9% for chloroethene-exposed and control groups, respectively before exposure. After exposure, however, there was a significant ($p<0.05$) increase in fetal loss among women whose husbands were exposed to chloroethene. Fetal loss was 15.8% and 8.8%, respectively among exposed and control groups with the age group, 25-29 years showing a larger increase (22.9% vs. 3.4% in controls).

The incidence of anencephaly, spina bifida and nydrocephalus among infants born to parents residing in the area of a PVC plant led Edmonds et al. (1978) to conduct a case-control study to examine the possible correlation between chloroethene exposure and the malformations. Based on an analysis of parental occupation and residence with respect to the plant, no relationship could be established between the cases of CNS malformations and exposure to chloroethene.

Th'eriault et al. (1983) examined the possible association between a high incidence of birth defects among infants born to residents of a town that had a potential exposure to chloroethene due to the presence of a vinyl chloride polymerization plant. The occurrence of defects appeared to fluctuate seasonally as did environmental chloroethene levels. Mothers of children with birth defects appeared to be younger than those in comparable communities. An analysis of occupation and residence of the parents did not show an association between birth defects and exposure to chloroethene.

5.4. OTHER REPRODUCTIVE EFFECTS

Anderson et al. (1977) conducted a dominant lethal assay of chloroethene using CD-1 male mice and examined their fertility after exposure. Exposure was at 3000, 10,000 and 30,000 ppm (7669, 25,562 and 76,687 mg/m^3) on 6 hours/day for 5 days. Males were mated for 8 weeks after treatment. The number of mated females that became pregnant was comparable between all dose groups and controls throughout the 8-week mating period.

5.5. CHRONIC TOXICITY

A 12-month inhalation toxicity study of chloroethene was conducted by Lee et al. (1977a) using CD-1 mice and CD rats. Groups of 36 animals of each sex and species were exposed at 0, 50, 250 or 1000 ppm (0, 128, 639 or 2556 mg/m^3) for 6 hours/day, 5 days/week. Interim sacrifices of 4 animals per sex, species and exposure level were scheduled at 1, 2, 3, 6 and 9 months with the remaining survivors sacrificed at 12 months. Food consumption, body weight, hematological and clinical chemistry determinations were made throughout the study. When moribund or at scheduled sacrifice intervals, animals were killed and necropsied for examination of all major organs. Tumors, abnormal growths and other lesions were prepared and examined microscopically. Tumors developed at an increased incidence among male and female mice exposed to all levels of chloroethene compared to controls (see Table 5-4, Section 5.1.). Mice exposed to 50 ppm also showed some toxic effects (rough hair coat, weight loss, lethargy, anorexia) and unscheduled deaths (occurring between the 6th and 12th month), which may or may not have been tumor-induced. Other toxic effects (non-neoplastic) among mice exposed to 50 ppm were not reported. In rats, an increased incidence of tumors occurred only in groups exposed to 250 and 1000 ppm (see Table 5-4). Two females exposed to 50 ppm died during the study (due to apparent toxic effects (lethargy, weight loss, lost muscular tone). No other toxic effects or changes in clinical chemistry or hematology occurred among the rats exposed at 50 ppm chloroethene.

In a three-part chronic inhalation toxicity study of chloroethene, Feron and coworkers (Feron et al., 1979a,b; Feron and Kroes, 1979) exposed Wistar rats to 5000 ppm (12,781 mg/m³) 7 hours/day, 5 days/week for 52 weeks. Toxic effects observed during the exposure period included slightly reduced growth rate, increased serum potassium levels, increased blood urea nitrogen, slight anemia, slightly shortened blood clotting time and increased mortality. At necropsy, kidney, heart and spleen weights were increased. Hepatic changes, tubular nephrosis, focal degeneration of the heart and increased hematopoietic activity of the spleen were observed histologically. Hepatic morphological changes included degenerative, hyperplastic and neoplastic (hepatocellular carcinoma and angiosarcoma) lesions.

Viola (1970) conducted a 12-month inhalation study of chloroethene at 0 or 30,000 ppm (76,687 mg/m³) in male Wistar rats. Groups of 25 animals were exposed for 4 hours/day on 5 days/week for the 12-month period. Histological examinations after sacrifice were performed on the brain, liver, kidneys, thyroid and paws of the rats. Diffuse degeneration of the grey and white matter of the cerebrum and cerebellum atrophy were observed in the exposed rats. Hepatic changes included diffuse interstitial inflammation, proliferation (hypertrophy) of Kupffer's cells and partial necrosis. Tubulonephrosis and chronic interstitial nephritis were characterized in the kidneys. The thyroid had an increase in parafollicular cells. Effects noted upon examination of the paws included metaplasia of the metatarsal bones, chondroid metaplasia, epidermal hyperkeratosis, basal layer vacuolization and degeneration, and general epidermal edema. No similar abnormalities were observed in the visceral organs, skeletal elements or skin in control group animals.

Chronic inhalation toxicity studies of chloroethene at levels of 50-500 ppm (128-1278 mg/m³) have been conducted by Torkelson et al. (1961) in rats, rabbits, guinea pigs and dogs. In the first experiment a group of 10 rats of each sex were exposed to 500 ppm chloroethene (1278 mg/m³) for 7 hours/day on 5 days/week for 4.5 months. Controls consisted of five rats of each sex. Exposure at 500 ppm (1278 mg/m³) resulted in increased average liver weights in both sexes (significant, $p=0.001$, only in males), centrilobular granular degeneration in the liver and tubular and interstitial changes in the kidney of treated rats. A second experiment was conducted using rats (20-24 of each sex/group), guinea pigs (10 males, 8 females/group), rabbits (3/sex/group), guinea pigs (10 males, 8 females/group), rabbits (3/sex/group) and dogs (1/sex/group) exposed at 100 or 200 ppm chloroethene (256 or 511 mg/m³) for 7 hours/day, 5 days/week for 6 months. Unexposed and air exposed controls were included. In rats, significantly ($p<0.005$) increased liver weights occurred in males and females exposed at both chloroethene levels. In rabbits exposed at 200 ppm (511 mg/m³) hepatotoxic effects were observed with centrilobular granular degeneration in both sexes, necrosis with foamy vacuolization in males and necrosis with periportal cellular infiltration in females. In a third experiment, rats (24/sex), guinea pigs (12/sex), rabbits (3/sex) and dogs (1/sex) were exposed to 50 ppm (128 mg/m³) for 7 hours/day, 5 days/week for 6 months. Additional groups of male rats ($n=10$/group) were exposed at 50 ppm for 1, 2 or 4 hours/day, 5 days/week for 6 months. Exposure at 50 ppm had no apparent toxic effects on any species in regard to mortality, growth and gross or microscopic organ examination compared to unexposed or air exposed controls.

Lee et al. (1978) and Hong et al. (1981) conducted a bioassay of chloroethene in CD-1 mice and CD rats exposed by inhalation at 0, 50, 250 or 1000 ppm (0, 128, 639 or 2556 mg/m³) for 6 hours/day, 5 days/week for 1, 3 or 6 months (mice) or 1, 3, 6 or 10 months (rats). Following exposure all groups were subsequently maintained for a 12-month observation period. Groups consisted of 8-28 mice of each sex, and 4-16 rats of each sex per duration and exposure level. In mice the mortality rate was increased for all duration and exposure level groups. Mortality among mice exposed at 250 and 1000 ppm (639 and 2556 mg/m³) was correlated with the cumulative tumor incidence (see Table 5-5) while no increased incidence of tumors occurred among mice exposed at 50 ppm (128 mg/m³). Mortality among the low-dose group (15/16 for those exposed for 6 months vs. 11/56 in controls) was therefore regarded as a toxic effect. The mortality rate for males and females combined in the control group and the 50 ppm group exposed for 10 months was 13/32 and 17/26, respectively.

The chronic toxicity of chloroethene inhaled at 0, 50, 500 and 20,000 ppm (0, 128, 1278 and 51,125 mg/m³), 5 hours/day, 5 days/week for 10 months was studied by Sokal et al. (1980) using male Wistar rats (85/group). Exposure at all chloroethene levels resulted in toxic effects which included decreased body weight, increased relative organ weights (heart, spleen, kidney, and liver), slight changes in blood chemistry and morphological changes in the liver and testes. Specifically among rats exposed at 50 ppm, heart and spleen weights were increased and nuclear polymorphism of hepatocytes was slightly increased.

The toxic effects of chronic chloroethene inhalation on the liver were examined by Wisniewska-Knypl et al. (1980) using male Wistar rats. Groups of 35-40 animals were exposed at 0, 50, 500 or 20,000 ppm (0, 128, 1278 or 51,125 mg/m³) chloroethene for 5 hours/day, 5 days/week for up to 10 months. Interim kills of 7-10 animals/exposure group were conducted at 1, 3 and 6 months. In rats exposed at 500 and 20,000 ppm, liver enlargement was evident with decreased microsomal cytochrome p-450 content within 3 months of exposure. Electron microscopic examination revealed concurrent hepatocellular changes ranging from smooth endoplasmic reticular proliferation in rats exposed at 50 ppm (128 mg/m³) to hypertrophic smooth endoplasmic reticulum, swelled mitochondria, increased lipid droplets and cytoplasmic degradation following exposure at 20,000 ppm (51,125 mg/m³).

The nonneoplastic effects of chronic chloroethene inhalation on the lung were examined in mice exposed at 2500 and 6000 ppm (6391 and 15,337 mg/m³), 5 hours/day, 5 days/week for 5 and 6 months (Suzuki, 1980). Toxic effects seen in both dose groups included bronchiolar epithelial proliferation and hypertrophy and hyperplastic alveolar epithelium (which also developed into alveologenic tumors; Section 5.1.).

The chronic toxicity of chloroethene following oral administration was studied by Feron et al. (1975) in male and female Wistar rats. Chloroethene was dissolved in soybean oil and administered by gavage to groups of 15 males and 15 females at approximate doses of 0, 30, 100 and 300 mg/kg bw on 6 days/week for 13 weeks. Behavior, body weights and food intake were not affected by chloroethene ingestion at any dose level. Liver weights showed a dose-related increasing trend in males and females but were significantly elevated ($p<0.05$) only in the high-dose group. Adrenal weight in males showed a dose-related decreasing trend. Hyperbasophilia of hepatocytes with ultrastructural changes were seen in the livers of rats exposed at the high-dose level. There was, however, no clinical evidence of hepatic damage as determined by liver enzyme assays.

The Dow Chemical Company (1984) conducted a 149-week study in which chloroethene was administered to Wistar rats as dietary powdered PVC fortified with the monomer. Gastrointestinal digestion apparently liberated almost all of the available chloroethene. Dietary levels were established to give doses of 0.0, 0.014, 0.13 and 1.3 mg chloroethene/kg bw/day. In addition, a group of unexposed controls were housed separately from the other test groups. Groups consisted of 100 males and 100 females, except for the high-dose group which contained 50 rats of each sex. Additional groups of 10 rats/sex/dose level were maintained for interim sacrifices at 9 and 18 months. General health, behavior, body weight and food intake were not affected by chloroethene exposure at any dose level tested. Mortality was slightly increased in the high-dose group. No changes in clinical chemistry parameters were reported. Hepatotoxic effects occurred among males and females exposed at 1.3 mg/kg/day. Liver changes included hepatocellular polymorphism, hepatic cysts, cellular alterations including clear cell foci (38/98 in males and females combined vs. 16/197 in controls) and basophilic foci (29/98 vs. 13/197 in controls). Neoplastic nodules (females) and hepatocellular carcinoma (males) were also increased among high-dose rats. In females, treated at 0.014 and 0.13 mg/kg/day there was also an increased incidence of basophilic foci of the liver (21/100 and 26/96, respectively, vs. 9/98 in controls).

In humans exposed occupationally to chloroethene a number of chronic toxic effects have been reported in addition to the carcinogenic effects (see Section 5.1.). In 1975, Lilis et al. (1975) reviewed some of the toxic effects in human workers exposed to chloroethene during the production of PVC. This review identified acroosteolysis and scleroderma (bone and skin changes of the phalanges), hepatotoxicity (hepatomegaly, tenderness and abnormal liver-function tests) and some pulmonary effects that were associated with exposure to chloroethene. Several recent studies (Destouet and Murphy, 1983; Black et al., 1983) have indicated that schleroderma and acroosteolysis are recognized toxic effects of chloroethene exposure.

Lilis et al. (1975) found that Raynaud's syndrome occurred in ~10% of workers with >20 years of exposure. Abnormal peripheral circulation (determined by the Allen test) was also found to be associated with length of exposure to chloroethene. Bone changes in the fingers and toes and hepatotoxic effects were confirmed among a group of 354 PVC workers (Lilis et al., 1975). Sakabe (1975) reviewed a number of reports on chloroethene-related symptoms among Japanese chloroethene production and PVC-production plants. This study confirmed the occurrence of acroosteolysis and Raynaud's syndrome among the Japanese companies.

The National Institute of Occupational Safety and Health (Waxweiler et al., 1977) conducted a survey of health effects among chloroethene-exposed workers from a PVC and rubber tire production plant. Based on exposure-level groupings there was an association between chloroethene exposure and the prevalence of hepatomegaly, CNS abnormalities, high blood pressure and fetal loss by spouses. There was no excess in acroosteolysis, Raynaud's syndrome, respiratory effects or chromosomal aberrations in exposed workers compared to a reference group of industrial workers. Lee et al. (1977b) detected no increased incidence of liver toxic effects or impaired liver function among a group of 422 PVC-production workers. Liver biopsies of 15 exposed workers revealed slightly increased fibrosis compared to 5 control workers. Tamburro et al. (1984) conducted a study of liver biopsies among 48 chloroethene workers and 30 nonchemical workers. Twenty-three of the exposed workers had hepatic lesions, which included focal hepatocyte hyperplasia (n=17), and more advanced mixed hyperplasias (n=6). In comparison, 5 of the reference group had hepatic lesions (4 focal hepatocyte hyperplasia, one mixed hyperplasia with sinusoid dilation). Doss et al. (1984) reported that porphyrinuria occurred among 36 workers exposed to chloroethene; this effect may be useful in clinical diagnosis of hepatic damage. Among a group of 200 chloroethene-production workers, Langauer-Lewowicka et al. (1983) reported that 54 had an astheno-autonomic syndrome and 88 showed the astheno-autonomic syndrome in addition to other neurological symptoms (pyramidal syndrome, cerebellum distrubances and trigeminal neuropathy). Scleroderma and Raynaud's syndrome were also prevalent among the chloroethene production workers. Neurological effects may have been due to direct toxic effects or as a result of vascular deficiency. Lloyd et al. (1984) conducted a case-control study of 265 workers exposed to chloroethene in the production of PVC and found an association between exposure and impaired lung function.

5.6. OTHER RELEVANT INFORMATION

There is a large body of data on the toxic effects of chloroethene following single or short-term exposures, primarily by inhalation (U.S. EPA, 1980). Many of the studies have been conducted to study the hepatotoxic effects and its progression to hepatic carcinogenicity (Drew et al., 1975; Reynolds et al., 1975; Jaeger et al., 1974, 1975; Conolly and Jaeger, 1977; Du et al., 1979; Bolt et al., 1979). In addition, a number of studies have examined the effects of hepatic enzyme inducers or simultaneous exposure to other toxicants on the acute toxicity of chloroethene (Drew et al., 1975; Reynolds et al., 1975; Jaeger et al., 1974, 1977; Conolly et al., 1978; Pessayre et al., 1979b). Pretreatment with phenobarbital or DDT appears to increase the formation of chloroethylene oxide by cytochrome p450 and also induces epoxide hydrase which inactivates the formed epoxide. Toxic effects appear to result when epoxide formation rates exceed the glutathione inactivation rate and the epoxide binds to liver cell components (proteins, nucleic acids) including cytochrome p450 (Conolly and Jaeger, 1979; Pessayre et al., 1979a). Pessayre et al. (1980) reported that 3-day exposures to chloroethene resulted in decreased cytochrome p450 concentrations and increased metabolites irreversibly bound to liver proteins.

In addition to the hepatotoxic effects associated with acute chloroethene exposure, inhalation exposure to 10,000-20,000 ppm (25,562-51,125 mg/m^3) caused decreased circulation and depressed contractibility with pulmonary resistance or bronchoconstriction (Aviado and Smith, 1975; Tatrai and Ungvary, 1981).

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

Few data on the responses of freshwater and marine organisms to chloroethene exposure were available for a comprehensive evaluation of aquatic toxicity. Brown et al. (1977) reported complete mortality of northern pike (*Esox lucius*) after a 10 day exposure to 388 ppm chloroethene. However, the descriptions of test methods and handling procedures for control and test organisms were incomplete. No difference could be detected between bacterial cultures of five bacterial populations and test cultures containing up to 900 mg/ℓ, indicating that chloroethene was not toxic to bacteria at these concentrations (Hill et al., 1976).

6.2. CHRONIC STUDIES

Samoiloff et al. (1980) investigated the effects of chloroethene on developmental stages of a nematode (*Panagrellus redivivus*) exposed at log concentrations of 0.000625-62.5 ppm. A 96-hour growth cycle was required to complete the development of the four life stages. Successful completion of each experimental growth stage at individual concentrations of chloroethene was compared to the control population by a 2x4 contingency analysis (X^2 test). Over the range of concentrations, the test organisms displayed little variation from the control group ($p<0.001$), indicating that chloroethene had little effect on the develomental success of *P. redivivus* at the concentrations tested.

6.3. OTHER RELEVANT INFORMATION

Additional information pertinent to the aquatic toxicity of chloroethene could not be located in the available literature as cited in the Appendix.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

Chloroethene is recognized as having carcinogenic potential in humans and has an assigned TLV at 5 ppm (~10 mg/m³) (ACGIH, 1985). The Occupational Safety and Health Administration (Code of Federal Regulations, 1981) has reported that no worker may be exposed to chloroethene at >1 ppm over an 8-hour period. A level of 5 ppm was the maximum level for a 15-minute exposure. Direct contact with liquid chloroethene is prohibited. There are standards for monitoring chloroethene and establishing regulated areas where exposure is expected. Various respiratory protection apparatus are required for exposures greater than the permissible exposure limits. The NIOSH (1975) reported that the concept of establishing a TLV for chloroethene gas was inappropriate based on its carcinogenic effects. The NIOSH, therefore, recommended that workers exposed to any measureable chloroethene should wear an air-supplied respirator.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of vinyl chloride could not be located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

Chloroethene has been recognized as a human and animal carcinogen by the IARC (1974, 1979, 1982) (IARC group 1) and the U.S. EPA (1980, 1984a,b). Unit risk estimates (q_1^*) for the carcinogenicity of chloroethene have been determined based on the available animal carcinogenesis data following oral and inhalation exposure (U.S. EPA, 1980, 1984a,b). Epidemiological evidence shows an increased risk of cancer development among chloroethene-exposed workers but does not provide sufficient exposure and incidence data to quantify risk based solely on human data.

Viola et al. (1971) reported the development of skin carcinoma, lung carcinoma and osteochondroma in rats exposed to chloroethene by inhalation to 30,000 ppm (76,687 mg/m³), 4 hours/day, 5 days/week for 12 months (see Table 5-1). Maltoni et al. (1980) conducted a battery of carcinogenicity tests on chloroethene administered by inhalation to rats, mice and hamsters. Inhalation exposure at 10 and 25 ppm (26 and 64 mg/m³), 4 hours/day, 5 days/week for 1 year produced liver angiosarcoma (1/119 and 5/120) and renal nephroblastoma (1/120) (spontaneously rare tumors) in rats, while mice developed liver and lung tumors at 250 ppm (639 mg/m³) (see Table 5-3). Hamsters developed forestomach tumors after inhaling chloroethene. Lee et al. (1977a, 1978) reported liver hemangiosarcomas and lung adenomas in mice exposed to chloroethene at 50, 250 and 1000 ppm (128, 639 or 2556 mg/m³), 6 hours/day, 5 days/week for 12 months (see Table 5-4). Rats treated on the same regimen developed liver and lung hemangiosarcomas at 250 and 1000 ppm (639 and 2556 mg/m³), while no tumors developed after treatment at 50 ppm (128 mg/m³). Hong et al. (1981) reported a low incidence of liver and lung tumors among mice treated at 50 ppm (128 mg/m³), 6 hours/day, 5 days/week for only 1 month. Greater tumor incidences occurred with longer exposure duration and/or higher exposure levels (see Table 5-5). In rats, liver and lung tumors developed as a result of treatment at 250 and 1000 ppm (639 and 2556 mg/m^3), while 50 ppm (128 mg/m^3) did not produce hepatic or pulmonary tumors. The Manufacturing Chemists Association (MCA, 1980) sponsored a carcinogenicity bioassay of chloroethene by inhalation at 50, 200 and 2500 ppm (128, 511 and 6391 mg/m^3), 6 hours/day, 5 days/week in rats and mice. In rats exposed for 12 months and observed for their lifetime, liver angiosarcoma and Zymbal gland tumors developed following treatment at all levels (see Table 5-7). Mice were exposed for 9 months and observed for their lifetime. Mice developed an increased incidence of liver angiosarcoma and lung alveolar adenomas and carcinomas following treatment at all dose levels compared to controls (see Table 5-7).

Studies by Hehir et al. (1981) and Suzuki (1981, 1983) have shown that even brief inhalation exposures to chloroethene cause the development of liver and lung tumors. Hehir et al. (1981) reported a dose-related increase in lung adenomas in mice exposed for a single 1-hour exposure at 50-50,000 ppm (128-127,812 mg/m^3) or ten 1-hour exposures at 500 ppm (1278 mg/m^3) (see Table 5-6). Suzuki (1981, 1983) reported a dose-related increase in pulmonary tumors among mice exposed at 1, 10 or 100 ppm (2.6, 26 or 256 mg/m^3), 5 hours/day, 5 days/week for 4 weeks. Data reported by Drew et al. (1983) suggest that the carcinogenic effect of chloroethene is diminished if animals are exposed after aging 12 months compared to young animals (see Table 5-8). This may be an artifact of the latency of tumor development.

In addition to the previously noted gavage study of chloroethene conducted by Maltoni (1977b) (see Table 5-2), Feron et al. (1981) and the

Dow Chemical Company (1984) have conducted oral carcinogenicity studies of chloroethene in which the compound was administered as PVC-containing diets or by gavage. Maltoni (1977b) reported that rats treated with chloroethene in olive oil by gavage at 16.65 or 50 mg/kg/day (5 days/week) for 1 year developed increased incidences of liver angiosarcoma and renal nephroblastoma (see Table 5-2). Liver hepatocellular carcinoma and angiosarcoma of the liver and lungs were reported in rats treated at 300 mg/kg/day by gavage or at 17.0, 5.6, or 1.8 mg/kg/day as PVC-containing diet (see Table 5-9) (Feron et al., 1981). The Dow Chemical Company (1984) administered PVC-containing diets to rats so that dose levels were 0.014, 0.13 and 1.3 mg chloroethene/kg/day. Rats treated at the highest dose level developed increased hepatic neoplastic nodules and preneoplastic foci while most effects were noncarcinogenic.

Monson et al. (1974) reported an 11-fold increase in hepatic or biliary cancer or both among chloroethene workers compared to expected numbers. In addition, brain cancer, lung cancer, digestive tract cancer and hematopoietic system cancers were increased among the chloroethene workers (see Table 5-10). Waxweiler et al. (1976) reported similar results among another group of chloroethene workers with increased liver/biliary, brain, respiratory tract and hematopoietic system cancers (see Table 5-11). Byren et al. (1976; see Table 5-12) reported increased liver, brain and lung cancer deaths among Swedish chloroethene and PVC-production workers. Fox and Collier (1977) reported an increased incidence of liver cancer deaths among PVC-production workers (see Table 5-13). Among Japanese chloroethene and PVC-production workers the total number of cancer deaths and liver cancer deaths were increased (Nakamura, 1983; see Table 5-14). Recently, Heldaas et al. (1984) reported increases in total cancer deaths, malignant melanoma, lung cancer, thyroid cancer and colon cancer among chloroethene and PVC production workers (see Table 5-15). The small number of cancer deaths (n=23) limited a clear exposure-related conclusion, but the authors noted that most cancers occurred among workers categorized as having high exposure.

In summary, chloroethene has been shown to be a carcinogen in several species of laboratory rodents producing a high incidence of liver, kidney, lung, brain and Zymbal gland tumors. A dose-related carcinogenic response has been shown following inhalation and oral exposure. A similar carcinogenic effect has been shown in humans with increased deaths due to liver, brain, lung and hematopoietic systems among chloroethene-exposed workers. The carcinogenicity unit risk estimate (q_1*) for humans exposed to chloroethene by ingestion of contaminated water was determined to be 1.74×10^{-2} $(mg/kg/day)^{-1}$ (U.S. EPA, 1980). This slope parameter was calculated based on the incidence of total tumors among rats exposed by inhalation at 50-10,000 ppm (128-25,562 mg/m^3) (Maltoni and Lefemine, 1975). A correction was made for the relationship between inhalation (ppm) and oral (mg/kg/day) dose levels. The q_1* was also corrected by the cube root of the ratio of the body weight of humans to the body weight of rats. The U.S. EPA (1984b) calculated a carcinogenic potency factor (q_1*) for humans based on the oral intubation study by Maltoni (1977b). The incidence of liver angiosarcoma was 0/150, 9/80 and 16/80 among rats treated at 0, 16.5 and 50 mg/kg/day (5 day/week) for 52 weeks (equivalent doses 0, 4.6 and 13.9 mg/kg/day). The q_1* was determined to be 1.4096×10^{-1} $(mg/kg/day)^{-1}$ after the cube root body weight ratio correction was made (U.S. EPA, 1984b).

More recent data reviewed in this document have shown carcinogenic effects at dose levels below those previously used for risk estimation and, therefore, would result in more conservative potency estimates of chloroethene carcinogenicity. Additional studies by Maltoni et al. (1980, 1981) tested the carcinogenicity of chloroethene in rats by inhalation exposure to 1-30,000 ppm (2.6-76,687 mg/m^3) for 4 hours/day, 5 days/week for 52 weeks (see Table 5-3). No carcinogenic effects were evident at chloroethene levels of $\leq$5 ppm (12.8 mg/m^3). At 10 ppm (26 mg/m^3) liver angiosarcoma occurred in 1/119 rats and liver angiosarcoma (5/120) and renal nephroblastoma (1/120) occurred at 25 ppm (64 mg/m^3). The dose-response data for liver angiosarcoma or kidney nephroblastoma could be used for the determination of a q_1* value for carcinogenic risk following inhalation exposure of chloroethene. Since the first liver angiosarcoma appeared at 10 ppm (26 mg/m^3), these data result in the highest (most conservative) estimate of carcinogenic risk of chloroethene (Table 8-1). The carcinogenic potency factor, q_1*, following inhalation exposure to chloroethene was determined to be 2.95×10^{-1} (mg/kg/day)$^{-1}$ using the GLOBAL computerization of the multistage model of carcinogenic risk (Howe and Crump, 1982). The unadjusted value was corrected by the cube root of the body weight ratio to give the human q_1*.

A carcinogenicity risk estimate for oral exposure to chloroethene can be calculated from dose-response data for lung and liver tumors reported by Feron et al. (1981) among rats exposed by dietary treatment. The U.S. EPA (1984a) calculated a carcinogenicity risk estimate for lifetime exposure to chloroethene through the drinking water. The estimated total incidence of lung and liver tumors in female rats treated with diets containing chloroethene-fortified PVC (Feron et al., 1981) were used to calculate a q_1* value for oral exposure to chloroethene (Table 8-2). The q_1* was determined to be 1.9 (mg/kg/day)$^{-1}$ using the GLOBAL computerization of the multistage model.

TABLE 8-1

Cancer Data Sheet for Derivation of q_1^*

Compound: Chloroethene

Reference: Maltoni et al., 1980, 1981

Species, Strain, Sex: Rat, Sprague-Dawley, M,F combined

Body weight: 0.35 kg (assumed)

Length of exposure (le) = 365 days

Length of experiment (Le) = up to 1029 days

Lifespan of animal (L) = 1029 days

Tumor site and type: Liver angiosarcoma

Route, vehicle: inhalation, air

Experimental Doses or Exposures		Transformed Dose[a]	Incidence
ppm	mg/m³	(mg/kg/day)	No. Responding/No. Tested or Examined
10	25.6	0.344	1/119
25	63.9	0.860	5/120
50	127.8	1.719	1/60
100	255.6	3.438	1/120
150	383.4	5.158	6/119
200	511.2	6.878	12/120
250	639.0	8.596	3/59
500	1278.1	17.19	6/60
2500	6390.5	86.97	13/60
6000	15337.4	206.3	13/59
10,000	25562.3	343.9	7/60
30,000	76687.1	1031.6	18/60
	Controls	0.0	0/363

Unadjusted q_1^* from study = 5.0381387×10^{-2} $(\text{mg/kg/day})^{-1}$[b]
Human q_1^* = 2.95×10^{-1} $(\text{mg/kg/day})^{-1}$

[a] $D = 0.223\ \text{m}^3\text{/day} \times 4/24 \times 5/7 \times [C] \times 0.5 \div 0.35 \times 365/1029$

[b] The unadjusted q_1^* was derived from the dose-response data up to doses of 1.719 mg/kg/day. The goodness of fit hypothesis was rejected for the data at ≥ 3.438 mg/kg/day.

TABLE 8-2

Cancer Data Sheet for Derivation of q_1*

Compound: Chloroethene

Reference: Feron et al., 1981

Species, Strain, Sex: Rat, Wistar, F

Body weight: 0.25 kg (assumed)

Length of exposure (le) = 1001 days

Length of experiment (Le) = 1001 days

Lifespan of animal (L) = 1001 days

Tumor site and type: Liver neoplastic nodules, hepatocellular carcinoma and angiosarcoma; lung angiosarcoma

Route, vehicle: oral, diet or soybean oil by gavage (high dose)

Experimental Doses or Exposures (mg/kg/day)	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Tested or Examined
17.0 (dietary, 7 days/week)	17.0	56/57
5.6 (dietary, 7 days/week)	5.6	42/59
1.8 (dietary, 7 days/week)	1.8	26/58
0.0 (dietary, 7 days/week) PVC powder only no chloroethene	0.0	2/57

Unadjusted q_1* from study = 0.294 $(mg/kg/day)^{-1}$
Human q_1* = 1.9 $(mg/kg/day)^{-1}$

The two q_1* values determined here, 2.95×10^{-1} (mg/kg/day)$^{-1}$ for inhalation exposure and 1.9 (mg/kg/day)$^{-1}$ for oral ingestion of chloroethene differ by a factor of ~8. This suggests that the oral route may be slightly more effective. These differences are relatively small considering that the data were generated by different research groups using different protocols. These q_1* values are >10-fold higher than that calculated by U.S. EPA (1980) based on the tumor incidences in rats exposed by inhalation to 128-25,562 mg/m^3 (Maltoni and Lefemine, 1975) and also higher than the q_1* calculated by U.S. EPA (1984b) based on the incidence of tumors in rats treated by gavage at 0-50 mg/kg/day (Maltoni, 1977b). Since chloroethene is activated through a saturable pathway it is important to limit the use of tumor response data for risk assessment to dose levels well below the saturation level of 200-250 ppm (V_{max}=110 μmol/kg/ha) (Bolt et al., 1977; Filser and Bolt, 1979; Hefner et al., 1975b). At higher doses the increase in concentration of active metabolite will not be linear, thus limiting the tumorogenic response. The dose levels used to derive the most recent q_1* values are below the saturable dose and therefore more likely to be in the linear dose response range than the previously developed q_1* values. Therefore, the higher q_1* values of 2.95×10^{-1} and 1.9 (mg/kg/day)$^{-1}$ are recommended for estimating the increased lifetime risk of cancer for human inhalation and oral exposure to chloroethene, respectively.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

The toxic effects of chronic exposure to chloroethene in animals and humans have been summarized in Section 5.5. of this document. A reportable quantity based on chronic toxicity of chloroethene has been previously determined by the U.S. EPA (1983b). Animals exposed by inhalation had toxic effects involving the liver, spleen, and kidneys with increased early mortality. Lee et al. (1977a) exposed rats and mice at 50, 250 and 1000 ppm (128, 639 and 2556 mg/m³) chloroethene 6 hours/day, 5 days/week for 12 months. Tumors developed in both species exposed at the two higher dose groups with toxic effects in mice (weight loss, lethargy, anorexia and increased mortality) exposed at 50 ppm. Feron et al. (1979a,b) and Feron and Kroes (1979) exposed rats at 5000 ppm (12,780 mg/m³) for 7 hours/day, 5 days/week for 52 weeks and reported toxic effects which included: slight growth retardation, hematological and blood chemistry changes, increased kidney spleen and heart weight, and increased mortality. Nonneoplastic histological changes were seen in the kidney, heart, spleen and liver with neoplastic effects in the liver. Inhalation exposure at 30,000 ppm (76,687 mg/m³) for 4 hours/day, 5 days/week for 12 months in rats resulted in hepatic histopathologies, including interstitial inflammation, Kupffer-cell hypertrophy and partial necrosis, and tubulonephrosis and nephritis of the kidneys (Viola, 1970). Cerebral and cerebellar atrophy was also noted among exposed rats. Examination of the paws of these rats revealed metatarsal bone metaplasia, chondroid metaplasia, basal cell degeneration and vacuolization, epidermal hyperkeritosis and edema. Torkelson et al. (1961) conducted several experiments exposing rats at 500 ppm (1278 mg/m³) and rats, guinea pigs, rabbits and dogs at 50, 100 and 200 ppm (128, 256 and 512 mg/m³) chloroethene 7 hours/day, 5 days/week for 4.5-6 months. No toxic effects were detected in any species following 6 months exposure at 50 ppm (128 mg/m³). Rats showed hepatotoxic effects at 100, 200 and 500 ppm (256, 511 and 1278 mg/m³) exposures while rabbits developed hepatotoxic effects (centrilobular granular degeneration, vacuolar degeneration and necrosis) at 200 ppm chloroethene. Lee et al. (1978) and Hong et al. (1981) exposed mice and rats to chloroethene at 50, 250 and 1000 ppm (128, 639 and 2556 mg/m³) for 6 hours/day, 5 days/week for up to 6 months (mice) or 10 months (rats) and allowed a 12-month observation period after exposure. The development of tumors among animals of both species exposed at 250 and 1000 ppm caused increased mortalities. Increased early mortality among mice and rats exposed at 50 ppm was regarded as a toxic effect since no tumor response occurred at this dose level. Sokal et al. (1980) reported increased heart and spleen weights and nuclear polymorphism of hepatocytes among rats exposed at 50 ppm (128 mg/m³) chloroethene (5 hours/day, 5 days/week) for 10 months. Suzuki (1980) reported toxic effects on the lungs, including bronchiolar and alveolar epithelial proliferation among mice exposed at 2500 and 6000 ppm (6391 and 15,337 mg/m³) for 5 hours/day, 5 days/week for 5 and 6 months.

Chronic toxic effects following oral exposure to chloroethene are seen primarily in the liver. Chloroethene was administered by gavage to rats at 30, 100 and 300 mg/kg on 6 days/week for 13 weeks causing increased liver weights and hyperbasophilic hepatocytes with ultrastructural changes at the high dose level (Feron et al., 1975). In the 149-week dietary administration study of chloroethene conducted by the Dow Chemical Company (1984), rats ingested chloroethene at 0.014, 0.13 and 1.3 mg/kg bw/day. Hepatotoxic effects developed in females exposed at all three levels (basophilic foci of the liver at low doses and more severe effects at the high dose group) while only males exposed at 1.3 mg/kg/day showed an increased incidence of liver histopathologies. Mortality was slightly increased among rats of the high dose group. Neoplastic nodules among females and hepatocellular carcinoma in males occurred in some rats of the high dose group.

In the available teratogenicity studies of chloroethene (John et al., 1977, 1981; Ungvary et al., 1978; Mirkova et al., 1978; Sal'nikova and Kitsovskaya, 1980) in mice, rats and rabbits, maternotoxic effects (reduced weight gain, mortality) and delayed fetal development occurred at similar exposure levels. Among mice exposed at 500 ppm (1278 mg/m^3) for 7 hours/day on days 6-15 of gestation fetal resorptions were increased, litter size decreased and fetal body weights reduced. Delayed ossification was reported in mice (500 ppm), rats (2500 ppm) and rabbits (500 ppm) exposed _in utero_ to chloroethene 7 hours/day but no developmental anomalies occurred (John et al., 1977, 1981). Ungvary et al. (1978) also reported increased fetal loss and resorptions among rats exposed (1500 ppm) during early gestation (days 1-9) but no malformations occurred after exposure during any trimester of gestation.

In humans, toxic effects associated with chronic occupational exposure to chloroethene include hepatotoxicity, acroosteolysis and schleroderma, Raynaud's syndrome and occasionally pulmonary effects. Several studies (Lilis et al., 1975; Sakabe, 1975; Destouet and Murphy, 1983; Black et al., 1983) have reported changes in the bones and skin of the phalanges possibly as a result of abnormal peripheral circulation among chloroethene-exposed workers. Waxweiler et al. (1977) reported a prevalence of hepatomegaly, high blood pressure and abnormalities of the CNS function among a cohort of chloroethene-exposed workers. Tamburro et al. (1984) also reported an increase in hepatic lesions (primarily focal hepatocyte hyperplasia) among liver biopsy specimens of chloroethene workers. Langauer-Lewowicka et al. (1983) reported frequent cases of astheno-autonomic syndrome and other neurological symptoms in addition to scleroderma and Raynaud's syndrome among a group of 200 chloroethene-production workers. These chronic toxic effects in humans are useful in qualitatively assessing the toxicity of chloroethene but due to the lack of sufficient exposure data, are inadequate for quantification of a dose-response relationship. Therefore they are inadequate for the derivation of a reportable quantity.

A summary of chronic toxicity studies of chloroethene in animals deemed adequate for quantitation of toxic effects, is presented in Table 9-1. The dose in mg/kg/day were calculated by expanding the inhalation exposure over a 24-hour day and a 7-day week, by multiplying by the animal inhalation rate and by dividing by the animal body weight. The values for inhalation rates used in the calculation were 0.039 m^3/day for mice, 0.223 m^3/day for rats (Federal Register, 1980) and 2.0 m^3/day for rabbits (U.S. EPA, 1985). The animal body weights were 0.03 kg for mice, 0.35 kg for rats (Federal Register, 1980) and 3.8 kg for rabbits (U.S. EPA, 1985). Studies of adequate experimental design and containing sufficient dose-response data for the determination of CSs and RQs are summarized in Table 9-2. The human MEDs were calculated by multiplying the animal dose by the cube root of the ratio of the animal body weight to the human body weight (70 kg) and by 70 kg to express the MED in mg/day. For short-term studies, the doses were divided by a factor of 10, as indicated on Table 9-2. The studies conducted by Lee and coworkers (Lee et al., 1977a; Lee et al., 1978; Hong et al., 1981) result in the highest CS and lowest RQ. In these studies mice and rats exposed to chloroethene at 50 ppm (128 mg/m^3) 6 hours/day, 5 days/ week for 12 months (Lee et al., 1977a) or 6 months followed by a 12-month latency had a higher rate of early mortality. Since tumor response at the exposure level was low, deaths were regarded as toxic effects. The exposure

TABLE 9-1

Toxicity Summary for Chloroethene

Route	Species/ Strain	Sex	No. at Start	Vehicle/ Physical State	Purity	Dosage/Exposure	Dose (mg/kg/day)	Response	Reference
Inhalation	mice/CD-1	M,F	72	air/vapor	99.8%	50 ppm ($128\ mg/m^3$) 6 hours/day, 5 days/week for 12 months	29.7	Mortality 20/72 vs. 2/72 in controls (may be tumor induced deaths)	Lee et al., 1977a
	rat/CD	M,F	72	air/vapor	99.8%	50 ppm ($128\ mg/m^3$) 6 hours/day, 5 days/week for 12 months	14.6	Mortality in females 2/36 vs. 0/36 in controls	Lee et al., 1977a
	rat/Wistar	M,F	124	air/vapor	NR	5000 ppm ($12,781\ mg/m^3$) 7 hours/day, 5 days/week for 52 weeks	1697	Reduced growth rate, increased blood urea nitrogen, slight anemia, shortened blood clotting time, increased mortality, increased organ weights and histological hepatic changes	Feron et al., 1979a,b; Feron and Kroes, 1979
	rat/Wistar	M	25	air/vapor	99%	30,000 ppm ($76,687\ mg/m^3$) 4 hours/day, 5 days/week for 12 months	5817	Cerebral degeneration; cerebellar atrophy. Hepatic hypertrophy, inflammation and partial necrosis. Tubulonephrosis and nephritis, proliferative changes of the bones, cartilage and epidermis of the paws	Viola, 1970
	rat/NR	M,F	40-48/ group	air/vapor	NR	50-500 ppm ($128\text{-}1278\ mg/m^3$) 7 hours/day, 5 days/week for 4.5-6 months	17.0-170	Increased liver weight with centrolobular degeneration at all levels except 50 ppm; No toxic effects at 50 ppm	Torkelson et al., 1961
	rabbit/NR	M,F	6/group	air/vapor		200 ppm ($511\ mg/m^3$) 7 hours/day, 5 days/week for 6 months	56.0	Hepatotoxicity with centrolobular degeneration and necrosis at 200 ppm	Torkelson et al., 1961
	mice/CD-1	M,F	16	air/vapor	99.8%	50 ppm ($128\ mg/m^3$) 6 hours/day, 5 days/week for 6 months	29.7	Mortality 15/16 vs. 11/50 in controls	Lee et al., 1978; Hong et al., 1981

TABLE 9-1 (cont.)

Route	Species/ Strain	Sex	No. at Start	Vehicle/ Physical State	Purity	Dosage/Exposure	Dose (mg/kg/day)	Response	Reference
Inhalation	rat/CD	M,F	26	air/vapor	99.8%	50 ppm (128 mg/m^3) 6 hours/day, 5 days/week for 10 months	14.6	Mortality 17/26 vs. 13/32 in controls	Lee et al., 1978; Hong et al., 1981
	rat/Wistar	M	85		99.7%	50 ppm (128 mg/m^3) 5 hours/day, 5 days/week for 10 months	12.1	Increased heart and spleen weight and nuclear polymorphism of liver cells	Sokal et al., 1980
	rat/Wistar		7		99.99%	500 ppm (1278 mg/m^3) 5 hours/day, 5 days/week for 10 months	121	Increased liver weight; ultrastructural hepatocyte changes	Wisniewska-Knypl et al., 1980
	mice/CD-1		17		NR	2500 ppm (6391 mg/m^3) 5 hours/day, 5 days/week for 5-6 months	1236	Bronchiolar and alveolar proliferative changes	Suzuki, 1980
Oral	rat/Wistar	M,F	30	soybean oil/ solution	NR	300 mg/kg 6 days/week for 13 weeks	257	Increased liver weight, hyperbasophilia of hepatocytes with ultrastructural changes	Feron et al., 1975
			100	PVC powder/ diet	99.97%	1.3 mg/kg/day for 149 weeks	1.3	Clear cell foci, basophilic foci, hepatocellular polymorphism of the liver, hepatic cysts	Dow Chemical Company, 1984
Inhalation	mice/CF-1	F	19 dams	air/vapor	NR	500 ppm (1278 mg/m^3) 7 hours/day on days 6-15 of gestation	485	Increased fetal resorptions, decreased litter size, decreased fetal body weight, delayed ossification	John et al., 1977, 1981
	rat/CFY	F	19 litters			4000 mg/m^3 continuously on days 1-9 of gestation	2549	Increased fetal loss due to resorptions	Ungvary et al., 1978

TABLE 9-2

Composite Scores for the Chronic Toxicity of Chloroethene

Route	Species	Animal Dose/Exposure (mg/kg/day)	Human MED (mg/day)	RV_d	Effect	RV_e	CS	RQ	Reference
Inhalation	mice	29.7 for 12 months	157	2.2	Increased early mortality	10	22	100	Lee et al., 1977a
Inhalation	rat	14.6 for 12 months	175	2	Slight increase in mortality in females	10	21	100	Lee et al., 1977a
Inhalation	rat	1697 for 12 months	20,313	1.0	Slight growth retardation; slightly shortened blood clotting time; increased potassium contents of the blood serum; increased kidney, heart and spleen weights; slight signs of anemia; tubular nephrosis; mild focal degeneration of the myocardium; increased hematopoietic activity in the spleen; degenerative, hyperplastic and neoplastic changes in liver parenchyma	7	7	1000	Feron et al., 1979a,b; Feron and Kroes, 1979
Inhalation	rat	5817 for 12 months	69,629	1.0	Metatarsal bone metaplasia; chondroid metaplasia; epidermal hyperkeratosis, basal layer vacuolization and degeneration, disappearance of the cutaneous adnexa and epidermal edema of the skin of the paw; diffuse degenerative lesions of the grey and white matter of the brain; atrophy of the granular layer of the cerebellum; livers were marked by an increased volume, diffused interstitial hepatitis, abnormal proliferation of Kupffer's cells and partial necrosis; kidney marked by tubulonephrosis sometimes accompanied by chronic interstitial nephritis; colloid goiter and increase in parafollicular cells of the thyroid	8	8	1000	Viola, 1970
Inhalation	rats	170 for 4.5 months	203*	2.0	Central lobular granular degeneration in the liver; interstitial and tubular changes in the kidneys; increased mean liver weight	6	12	1000	Torkelson et al., 1961
Inhalation	rats	33.9 for 6 months	40.5*	3.1	Increased mean liver weight	4	12.4	1000	Torkelson et al., 1961
Inhalation	rabbit	56.0 mg/m³ for 6 months	148*	2.2	Central lobular granular degeneration in the liver; necrosis with foamy vacuolization in males and necrosis with periportal cellular infiltration in females	7	15.6	1000	Torkelson et al., 1961

TABLE 9-2 (cont.)

Route	Species	Animal Dose/Exposure (mg/kg/day)	Human MED (mg/day)	RV_d	Effect	RV_e	CS	RQ	Reference
Inhalation	mouse	29.7 x 6 months, plus 12 months observation	157	2.2	Increased mortality or moribundity during observation period	10	22	100	Lee et al., 1978; Hong et al., 1981
Inhalation	rats	14.6 for 10 months, plus 12 months observation	175	2.1	Slightly increased mortality or moribundity during exposure and observation period	10	21	100	Lee et al., 1978; Hong et al., 1981
Inhalation	mouse	1236 for 5 or 6 months	652*	1.3	Proliferation and hypertrophy of the terminal bronchiolar cells, hyperplasia of alveolar epithelium, degeneration of alveolar septa cells, occasional inflammation	7	9.1	1000	Suzuki, 1980
Inhalation	rat	12.1 for 10 months	145	2.3	Increased heart and spleen weights, hepatocyte nuclear polymorphism	2	4.6	5000	Sokal et al., 1980
Inhalation	rat	121 for 10 months	1,440	1.0	Increased liver weight, ultrastructural hepatocyte changes	4	4	5000	Wisniewska-Knypl et al., 1980
Oral	rat	257 for 13 weeks	300*	1.0	Increased liver weight, hyperbasophilia of hepatocytes with ultrastructural changes	4	7	1000	Feron et al., 1975
Oral	rat	1.3 for 149 weeks	15.6	3.7	Clear cell foci, basophilic foci in liver, hepatocellular polymorphism, and hepatic cyst	5	10.5	1000	Dow Chemical Company, 1984
Inhalation	mice	485 on days 6-15 of gestation	2,560	1.0	Increased fetal resorptions, decreased litter size, decreased fetal body weight, delayed ossification	8	8	1000	John et al., 1977, 1981
Inhalation	rats	2549 on days 1-9 of gestation	30,511	1.0	Significantly increased fetal mortality and fetotoxic effects	8	8	1000	Ungvary et al., 1978

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*An uncertainty factor of 10 was applied to convert from a subchronic animal exposure to a chronic human MED.

exposure level in mice leads to a human MED of 157 mg/day. The RV_d would be 2.2, and based on increased mortality as the toxic effect an RV_e of 10 is used. The resulting CS (RV_dxRV_e) would be 22 and the appropriate RQ is 100. In rats, the same effective exposure level results in a higher human MED but essentially the same RV_d. The slight increase in mortality rate warrants a RV_e of 10 and the resultant CS and RQ are 21 and 100, respectively (see Table 9-2). The highest CS and lowest RQ, those derived from toxicity data in mice reported by Lee et al. (1977a, 1978) and Hong et al. (1981), were chosen as the most conservative representation of the toxicity of chronic exposure to chloroethene (Table 9-3).

In the previous determination of the RQ (U.S. EPA, 1983b), the same study was used as the basis of the RQ; however, the MED was larger, resulting in a lower RV_d, and hence a lower CS of 20, which corresponds to an RQ of 1000. In the present determination, the more conservative RQ of 100 resulted because of differences in the method of deriving the MED. In the previous document, inhalation exposures were considered to be equivalent among species; therefore, the inhalation exposure was converted directly to a human MED by multiplying by the human inhalation rate and assuming and absorption efficiency of 50%. In the current methodology, animal exposures are converted to animal doses, which are corrected by the cube root of the body weight ratio.

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

The available carcinogenicity data on chloroethene are reviewed in Section 5.1. of this document and the studies are summarized in Tables 9-4 to 9-18. The evaluation of carcinogenic potential of chloroethene (vinyl chloride) and derivation of a potency factor (F-factor) has been done previously by the U.S. EPA (1983a).

TABLE 9-3

Chloroethene

MINIMUM EFFECTIVE DOSE (MED) AND REPORTABLE QUANTITY (RQ)

Route:	inhalation
Dose*:	157 mg/day
Effect:	increased mortality and moribundity
Reference:	Lee et al., 1977a, 1978; Hong et al., 1981
RV_d:	2.2
RV_e:	10
Composite Score:	22
RQ:	100

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*Equivalent human dose

TABLE 9-4

Bioassay Data for Male Wistar Rats (Ar/IRE) Exposed to Chloroethene by Inhalation for 12 months[a]

Dose or Exposure[b] (ppm)	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
30,000	>12 months[c]	99%	vapor/air	skin	epidermoid carcinoma	15/26
				lung	carcinoma	6/26
				bone	osteochondroma	5/26
0	>12 months[c]	NA	air only	skin	epidermoid carcinoma	0/25
				lung	carcinoma	0/25
				bone	osteochondroma	0/25

QUALITY OF EVIDENCE

Strengths of Study: An appropriate route of administration was used. The chloroethene was relatively pure. Appropriate controls were included for comparison.

Weakness of Study: Only male mice were tested. The duration of the study could have been longer. No statistics were compiled on incidences between treated and untreated animals.

Overall Adequacy: Adequate

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[a] Source: Viola et al., 1971

[b] Exposure was for 4 hours/day, 5 days/week for 12 months.

[c] Surviving animals were killed at 20-day intervals following treatment.

NA = Not applicable

TABLE 9-5

Bioassay Data for Sprague-Dawley Rats Exposed to Chloroethene for 52 weeks[a,b]

Exposure Route	Sex	Dose or Exposure[c]	Duration of Study (weeks)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
Inhalation	NR	10,000 ppm	155	vapor/air	liver kidney	angiosarcoma nephroblastoma	9/60 5/60
		6,000 ppm	155	vapor/air	liver kidney	angiosarcoma nephroblastoma	13/60 4/60
		200 ppm	143	vapor/air	liver	angiosarcoma	12/120
		150 ppm	143	vapor/air	liver	angiosarcoma	5/120
		100 ppm	143	vapor/air	liver	angiosarcoma	1/120
		0 ppm	143-155	air only	liver kidney	angiosarcoma nephroblastoma	0/500 0/120
Oral (gavage)	NR	50 mg/kg	136	olive oil	liver kidney	angiosarcoma nephroblastoma	16/80 2/80
		16.65 mg/kg	136	olive oil	liver kidney	angiosarcoma nephroblastoma	9/80 3/80
	M,F	0.0 mg/kg	136	olive oil only	liver kidney	angiosarcoma nephroblastoma	0/150 0/150

QUALITY OF EVIDENCE

Strengths of Study:	A broad range of dose levels were tested. Carcinogenic response was shown by two routes of administration. Duration of study was long in all cases.
Weakness of Study:	No statistics were reported. The sex of test animals is not reported. Data for the control group for the gavage studies is reported in Maltoni et al., 1981. Animals treated by gavage. The purity of the chloroethene is not reported.
Overall Adequacy:	Adequate
Comments:	This study focused on different factors affecting the carcinogenic effect (animal species, strain and age, treatment duration, and exposure levels).

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[a] Source: Maltoni, 1977b

[b] Purity of compound not reported

[c] Exposure to chloroethene by inhalation was for 4 hours/day, 5 days/week for 52 weeks; by gavage once daily in olive oil 4-5 days/week.

NR - Not reported

TABLE 9-6

Animal Bioassay Data for Inhalation Exposure to Chloroethene[a,b]

Species/ Strain	Sex	Dose or Exposure[c] (ppm)	Duration of Treatment (weeks)	Duration of Study (weeks)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
Rat/ Sprague-Dawley	M,F	30,000	52	68	air/vapor	liver kidney	angiosarcoma nephroblastoma	18/60 NR
		10,000	52	135	air/vapor	liver kidney	angiosarcoma nephroblastoma	7/60 5/60
		6,000	52	135	air/vapor	liver kidney	angiosarcoma nephroblastoma	13/59 5/59
		2,500	52	135	air/vapor	liver kidney	angiosarcoma nephroblastoma	13/60 6/60
		500	52	135	air/vapor	liver kidney	angiosarcoma nephroblastoma	6/60 6/60
		250	52	135	air/vapor	liver kidney	angiosarcoma nephroblastoma	3/59 5/59
		200	52	143	air/vapor	liver kidney	angiosarcoma nephroblastoma	12/120 7/120
		150	52	143	air/vapor	liver kidney	angiosarcoma nephroblastoma	6/119 11/119
		100	52	143	air/vapor	liver kidney	angiosarcoma nephroblastoma	1/120 10/120
		50	52	135	air/vapor	liver kidney	angiosarcoma nephroblastoma	1/60 1/60
		25	52	147	air/vapor	liver kidney	angiosarcoma nephroblastoma	5/120 1/120
		10	52	147	air/vapor	liver kidney	angiosarcoma nephroblastoma	1/119 0/119
		5	52	147	air/vapor	liver kidney	angiosarcoma nephroblastoma	0/119 0/119

TABLE 9-6 (cont.)

Species/ Strain	Sex	Dose or Exposure^c (ppm)	Duration of Treatment (weeks)	Duration of Study (weeks)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
Rat/ Sprague-Dawley	M,F	1	52	147	air/vapor	liver kidney	angiosarcoma nephroblastoma	0/118 0/118
		0	NA	135-147	air only	liver kidney	angiosarcoma nephroblastoma	0/363 0/363
Mouse/ Swiss	M,F	10,000	30	81	air/vapor	liver lung	angiosarcoma tumor	10/56 45/56
		6,000	30	81	air/vapor	liver lung	angiosarcoma tumor	13/60 47/60
		2,500	30	81	air/vapor	liver lung	angiosarcoma tumor	16/59 40/59
		500	30	81	air/vapor	liver lung	angiosarcoma tumor	14/60 50/60
		250	30	81	air/vapor	liver lung	angiosarcoma tumor	18/60 41/60
		50	30	81	air/vapor	liver lung	angiosarcoma tumor	1/60 6/60
		0	NA	81	air only	liver lung	angiosarcoma tumor	0/150 15/150
Hamster/ Syrian Golden	M,F	10,000	30	109	air/vapor	forestomach	papilloma/acanthoma	10/30
		6,000	30	109	air/vapor	forestomach	papilloma/acanthoma	10/30
		2,500	30	109	air/vapor	forestomach	papilloma/acanthoma	17/30
		500	30	109	air/vapor	forestomach	papilloma/acanthoma	9/30
		250	30	109	air/vapor	forestomach	papilloma/acanthoma	4/30

TABLE 9-6 (cont.)

Species/ Strain	Sex	Dose or Exposure^c (ppm)	Duration of Treatment (weeks)	Duration of Study (weeks)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
Hamster/ Syrian Golden		50	30	109	air/vapor	forestomach	papilloma/acanthoma	3/30
		0	NA	109	air only	forestomach	papilloma/acanthoma	3/60

QUALITY OF EVIDENCE

Strengths of Study: Chloroethene was administered by inhalation to rats, mice, and hamsters at a broad range of doses. Extensive examinations of animals were performed. Duration of studies was long.

Overall Adequacy: Adequate

Comments: This report was extensive and much of the data was not reported here due to the scope of this project.

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[a]Source: Maltoni et al., 1981

[b]Purity of compound was >99.9%

[c]Exposure was for 4 hours/day, 5 days/week

NA = Not applicable

TABLE 9-7

Animal Bioassay Data for Inhalation Exposure to Chloroethene for 12 months[a,b]

Species/ Strain	Sex	Dose or Exposure[c] (ppm)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
Rat/CD	M	50	vapor/air	liver	hemangiosarcoma	0/36
				lung	hemangiosarcoma	0/36
	F	50	vapor/air	liver	hemangiosarcoma	0/36
				lung	hemangiosarcoma	0/36
	M	250	vapor/air	liver	hemangiosarcoma	2/36
				lung	hemangiosarcoma	0/36
	F	250	vapor/air	liver	hemangiosarcoma	10/34 ($p<0.05$)
				lung	hemangiosarcoma	3/34
	M	1000	vapor/air	liver	hemangiosarcoma	6/34
				lung	hemangiosarcoma	4/34
	F	1000	vapor/air	liver	hemangiosarcoma	15/36 ($p<0.05$)
				lung	hemangiosarcoma	9/36
	M	0	air only	liver	hemangiosarcoma	0/35
				lung	hemangiosarcoma	0/35
	F	0	air only	liver	hemangiosarcoma	0/35
				lung	hemangiosarcoma	0/35

TABLE 9-7 (cont.)

Species/ Strain	Sex	Dose or Exposure^c (ppm)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
Mouse/CD-1	M	0	air only	respiratory tract	bronchioloalveolar adenoma	1/26
				liver	hemangiosarcoma	0/26
	F	0	air only	respiratory tract	bronchioloalveolar adenoma	0/36
				liver	hemangiosarcoma	0/36
	M	50	vapor/air	respiratory tract	bronchioloalveolar adenoma	8/29
				liver	hemangiosarcoma	3/29
	F	50	vapor/air	respiratory tract	bronchioloalveolar adenoma	4/34
				liver	hemangiosarcoma	0/34
	M	250	vapor/air	respiratory tract	bronchioloalveolar adenoma	10/29
				liver	hemangiosarcoma	7/29 (p<0.05)
	F	250	vapor/air	respiratory tract	bronchioloalveolar adenoma	12/34
				liver	hemangiosarcoma	16/34 (p<0.05)

TABLE 9-7 (cont.)

Species/ Strain	Sex	Dose or Exposure^c (ppm)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
Mouse/CD-1	M	0	air only	respiratory tract	bronchioloalveolar adenoma	1/26
				liver	hemangiosarcoma	0/26
	F	0	air only	respiratory tract	bronchioloalveolar adenoma	0/36
				liver	hemangiosarcoma	0/36
	M	50	vapor/air	respiratory tract	bronchioloalveolar adenoma	8/29
				liver	hemangiosarcoma	3/29
	F	50	vapor/air	respiratory tract	bronchioloalveolar adenoma	4/34
				liver	hemangiosarcoma	0/34
	M	250	vapor/air	respiratory tract	bronchioloalveolar adenoma	10/29
				liver	hemangiosarcoma	7/29 ($p<0.05$)
	F	250	vapor/air	respiratory tract	bronchioloalveolar adenoma	12/34
				liver	hemangiosarcoma	16/34 ($p<0.05$)

TABLE 9-7 (cont.)

Species/ Strain	Sex	Dose or Exposure[c] (ppm)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
Mouse/CD-1	M	1000	vapor/air	respiratory tract	bronchioloalveolar adenoma	12/33
				liver	hemangiosarcoma	13/33 ($p<0.05$)
	F	1000	vapor/air	respiratory tract	bronchioloalveolar adenoma	26/36
				liver	hemangiosarcoma	18/36 ($p<0.05$)

QUALITY OF EVIDENCE

Strengths of Study: Three different dose levels of chloroethene were tested by inhalation in two species of animals. Some statistics were reported. Chloroethene was quite pure. An extensive examination of organs and tissues was performed..

Weakness of Study: The significance of bronchioloalveolar adenoma in mice is not reported. The duration of study was short (due to morality).

Overall Adequacy: Adequate

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[a] Source: Lee et al., 1978

[b] Purity of compound was 99.8%

[c] Exposure was for 6 hours/day, 5 days/week for 12 months

TABLE 9-8

Animal Bioassay Data for Inhalation Exposure to Chloroethene[a,b]

Species/ Strain	Sex	Dose or Exposure[c] (ppm)	Duration of Treatment (months)	Duration of Study (months)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
Rat/CD	M,F	50	6 or 10[d]	18 or 22[d]	air/vapor	liver	hepatocellular carcinoma	0/66
							hemangiosarcoma	0/66
						lung	bronchioloalveolar tumor	0/66
							hemangiosarcoma	0/66
		250	6 or 10[d]	18 or 22[d]	air/vapor	liver	hepatocellular carcinoma	2/68
							hemangiosarcoma	5/68
						lung	bronchioloalveolar tumor	2/68
							hemangiosarcoma	2/68
		1000	6 or 10[d]	18 or 22[d]	air/vapor	liver	hepatocellular carcinoma	7/72
							hemangiosarcoma	14/72
						lung	bronchioloalveolar tumor	4/72
							hemangiosarcoma	7/72
		0	NA	18 or 22[d]	air only	lung	hemangiosarcoma	1/72
							hemangiosarcoma	0/72
							hemangiosarcoma	0/72
							hemangiosarcoma	0/72
Mouse/CD-1	M,F	50	1	13	air/vapor	lung	bronchioloalveolar tumor	3/32
						liver	hemangiosarcoma	1/32
		250	1	13	air/vapor	lung	bronchioloalveolar tumor	19/32
						liver	hemangiosarcoma	0/32
		1000	1	13	air/vapor	lung	bronchioloalveolar tumor	20/32
						liver	hemangiosarcoma	0/32
		0	NA	13	air only	lung	bronchioloalveolar tumor	3/32
						liver	hemangiosarcoma	0/32

TABLE 9-8 (cont.)

Species/ Strain	Sex	Dose or Exposure^c (ppm)	Duration of Treatment (months)	Duration of Study (months)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
Mouse/CD-1	M,F	50	3	15	air/vapor	lung	bronchioloalveolar tumor	12/32
						liver	hemangiosarcoma	0/32
		250	3	15	air/vapor	lung	bronchioloalveolar tumor	21/32
						liver	hemangiosarcoma	4/32
		1000	3	15	air/vapor	lung	bronchioloalveolar tumor	5/20
						liver	hemangiosarcoma	16/20
		0	NA	15	air only	lung	bronchioloalveolar tumor	2/32
						liver	hemangiosarcoma	0/32
		50	6	18	air/vapor	lung	bronchioloalveolar tumor	3/16
						liver	hemangiosarcoma	1/16
		250	6	18	air/vapor	lung	bronchioloalveolar tumor	16/20
						liver	hemangiosarcoma	9/20
		1000	6	18	air/vapor	lung	bronchioloalveolar tumor	14/24
						liver	hemangiosarcoma	13/24
		0	NA	18	air/vapor	lung	bronchioloalveolar tumor	11/56
						liver	hemangiosarcoma	1/56

TABLE 9-8 (cont.)

Species/ Strain	Sex	Dose or Exposure[c] (ppm)	Duration of Treatment (months)	Duration of Study (months)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence

QUALITY OF EVIDENCE

Strengths of Study:	Two animal splecies were tested. Dose and exposure levels were varied to show a dose-response. Statistics of tumor incidence with respect to dose are reported.
Weakness of Study:	The duration of treatment was too short in all cases.
Overall Adequacy:	Adequate
Comments:	This study was conducted to enhance that reported by Lee et al., 1978.

---

[a] Source: Hong et al., 1981

[b] Purity of compound was 99.8%

[c] Exposure was for 6 hours/day, 5 days/week

[d] Duration of exposure was for 6 or 10 months, followed by a 12-month latency period. The results presented are for the combined treatment-duration group.

NA = Not applicable

TABLE 9-9

Animal Bioassay Data for Inhalation Exposure to Chloroethene[a,b]

Species/ Strain	Sex	Dose or Exposure (ppm)	Duration of Treatment	Duration of Study	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
Mouse/ICR	M,F	50,000	1 day (1 hour)	18 months	air/vapor	lung	adenoma carcinoma	45/137 3/137
		5,000	1 day (1 hour)	18 months	air/vapor	lung	adenoma carcinoma	24/143 1/143
		500	1 day (1 hour)	18 months	air/vapor	lung	adenoma carcinoma	18/139 1/139
		50	1 day (1 hour)	18 months	air/vapor	lung	adenoma carcinoma	14/139 0/139
		0	NA	18 months	air/vapor	lung	adenoma carcinoma	12/120 0/120
Rat/F344	M,F	0, 50, 500, 5000, 50,000	1 day (1 hour)	lifetime	air/vapor	lung liver	malignant	0/178-190 per dose
Mouse/A/J	M,F	500	ten 1-hour exposures	20 months	air/vapor	lung	adenoma carcinoma	124/166 22/166
		0	NA	20 months	air only	lung	adenoma carcinoma	31/90 3/90
		50	100 1-hour exposures	20 months	air/vapor	lung	adenoma carcinoma	65/158 7/158
		0	NA	20 months	air only	lung	adenoma carcinoma	29/84 2/84
Rat/F344	M,F	500	ten 1-hour exposures	lifetime	air/vapor	lung liver	malignant malignant	0/180 0/180
		50	100 1-hour exposures	lifetime	air/vapor	lung liver	malignant malignant	0/180 0/180
		0	NA	lifetime	air only	lung liver	malignant malignant	0/100 0/100

TABLE 9-9 (cont.)

Species/ Strain	Sex	Dose or Exposure (ppm)	Duration of Treatment	Duration of Study	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence

QUALITY OF EVIDENCE

Strengths of Study:	Exposures were conducted at several exposure levels using rats and mice of both sexes.
Weakness of Study:	Exposures, except for 100 1-hour treatments at 50 ppm, were very brief. Lung adenomas are usually considered benign. The incidence of carcinomas was low and statistics were not performed. No carcinogenic effect was shown in rats.
Overall Adequacy:	Limited
Comments:	Pulmonary tumors occur spontaneously in A/J - mice and may not be a valid test for carcinogenicity.

[a] Source: Nehir et al., 1981

[b] Purity of compound not reported

NA = Not applicable

TABLE 9-10

Animal Bioassay Data for Inhalation Exposure to Chloroethene[a,b,c]

Species/ Strain	Sex	Dose or Exposure[d] (ppm)	Duration of Treatment	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
Rat/COBS	M,F	2500	12 months	air/vapor	liver Zymbal gland[e]	angiosarcoma tumor	114/147 12/13
		200	12 months	air/vapor	liver Zymbal gland[e]	angiosarcoma tumor	82/141 2/23
		50	12 months	air/vapor	liver Zymbal gland[e]	angiosarcoma tumor	28/139 3/14
		0	12 months	air only	liver Zymbal gland[e]	angiosarcoma tumor	0/143 0/25
Mouse/CDI Swiss	M,F	2500	9 months	air/vapor	liver lung	angiosarcoma alveolar adenoma alveolar carcinoma	101/101 101/101 18/101
		200	9 months	air/vapor	liver lung	angiosarcoma alveolar adenoma alveolar carcinoma	130/134 119/134 4/134
		50	9 months	air/vapor	liver lung	angiosarcoma alveolar adenoma alveolar carcinoma	46/121 92/120 10/120
		0	NA	air only	liver lung	angiosarcoma alveolar adenoma alveolar carcinoma	0/97 10/96 1/96
Hamster/ Golden Syrian	M,F	2500	12 months	air/vapor	liver	angiosarcoma	56/66
		200	12 months	air/vapor	liver	angiosarcoma	12/88
		50	12 months	air/vapor	liver	angiosarcoma	7/74
		0	12 months	air only	liver	angiosarcoma	0/83

TABLE 9-10 (cont.)

Species/ Strain	Sex	Dose or Exposure[d] (ppm)	Duration of Treatment	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence

QUALITY OF EVIDENCE

Strengths of Study:	Three species of animals, both sexes of each were exposed at three levels. Exposure was for 12 months and a long latency was allowed. Appropriate controls were maintained. Histological examination of major organs was conducted.
Overall Adequacy:	Adequate
Comments:	Tumors were reported as total number of tumors, therefore, tumor incidence reported here (tumor bearing animals/total animals examined)

---

[a] Source: MCA, 1980

[b] Duration of study was for lifetime

[c] Purity of compound was not reported

[d] Exposure was for 7 hours/day, 5 days/week

[e] Not all rats were examined for Zymbal gland tumors

NA = Not applicable

TABLE 9-11

Animal Bioassay Data for Inhalation Exposure to Chloroethene[a,b]

Species/ Strain	Sex	Dose or Exposure[c] (ppm)	Duration of Treatment (months)	Duration of Study (months)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
Rat/F344	F	100	6	24	air/vapor	liver	hemangiosarcoma	4/76[d]
							hepatocellular carcinoma	3/75
						mammary gland	fibroadenoma	28/76[d]
		100	12	24	air/vapor	liver	hemangiosarcoma	11/55[d]
							hepatocellular carcinoma	4/56[d]
						mammary gland	fibroadenoma	28/56[d]
		100	18	24	air/vapor	liver	hemangiosarcoma	13/55[d]
							hepatocellular carcinoma	8/54[d]
						mammary gland	fibroadenoma	24/55[d]
		100	24	24	air only	liver	hemangiosarcoma	19/55[d]
							hepatocellular carcinoma	9/54[d]
						mammary gland	fibroadenoma	26/55[d]
		0	NA	24	air only	liver	hemangiosarcoma	1/112
							hepatocellular carcinoma	1/112
						mammary gland	fibroadenoma	24/112
Hamster/ Golden Syrian	F	200	6	24	air/vapor	all sites	hemangiosarcoma	13/88[d]
						mammary gland	carcinoma	28/87[d]
						stomach	adenoma	23/88[d]
		200	12	24	air/vapor	all sites	hemangiosarcoma	4/52[d]
						mammary gland	carcinoma	31/52[d]
						stomach	adenoma	3/50[e]
		200	18	24	air/vapor	all sites	hemangiosarcoma	2/103
						mammary gland	carcinoma	47/102[d]
						stomach	adenoma	20/101[e]
		0	NA	24	air only	all sites	hemangiosarcoma	0/143
						mammary gland	carcinoma	0/143
						stomach	adenoma	5/138

TABLE 9-11 (cont.)

Species/ Strain	Sex	Dose or Exposure^c (ppm)	Duration of Treatment (months)	Duration of Study (months)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
Mouse/ B6C3F1	F	50	6	18	air/vapor	all sites mammary gland	hemangiosarcoma carcinoma	46/67^d 29/67^d
		50	12	18	air/vapor	all sites mammary gland	hemangiosarcoma carcinoma	69/90^d 37/90^d
	F	0	NA	24	air only	all sites mammary gland	hemangiosarcoma carcinoma	4/69 3/69
Mouse/ Swiss	F	50	6	18	air/vapor	all sites mammary gland lung	hemangiosarcoma carcinoma carcinoma	29/67^d 33/67^d 18/65^d
		50	12	18	air/vapor	all sites mammary gland lung	hemangiosarcoma carcinoma carcinoma	30/47^d 22/47^d 11/45^d
		0	NA	18	air only	all sites mammary gland lung	hemangiosarcoma carcinoma carcinoma	1/71^d 2/71^d 9/71^d

QUALITY OF EVIDENCE

Strengths of Study: The chloroethene was administered at a maximum tolerated dose. Several species of rodents were tested. Complete histopathological examinations were performed. Statistics were performed.

Weakness of Study: Only female animals were tested.

Overall Adequacy: Adequate

Comments: Additional tests by these authors showed little or no carcinogenic effect in rats and hamsters if chloroethene exposure was started after 12 months of non-exposure.

---

[a] Source: Dow et al., 1983

[b] Purity of compound not reported

[c] Exposure was for 6 hours/day, 5 days/week

[d] $p<0.01$

[e] $p<0.05$

NA = Not applicable; NR = not reported

TABLE 9-12

Bioassay Data for Male and Female Wistar Rats Exposed to Chloroethene[a,b,c]

Exposure Route	Dose or Exposure[d] (mg/kg/day)	Duration of Treatment (weeks)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
Oral (gavage)	300[d]	84	soybean oil	liver	hepatocellular carcinoma	1/109
					angiosarcoma	56/109
				lung	angiosarcoma	42/109
Oral (diet)	17.0	143	PVC	liver	hepatocellular carcinoma	37/117 (p<0.001)
					angiosarcoma	36/117 (p<0.001)
				lung	angiosarcoma	24/116
	5.6	143	PVC	liver	hepatocellular carcinoma	21/115
					angiosarcoma	8/115
				lung	angiosarcoma	5/115
	1.8	143	PVC	liver	hepatocellular carcinoma	5/116
					angiosarcoma	0/116
				lung	angiosarcoma	0/116
	0.0	NA	untreated diet only	liver	hepatocellular carcinoma	0/112
					angiosarcoma	0/112
				lung	angiosarcoma	0/112

TABLE 9-12 (cont.)

Exposure Route	Dose or Exposure[d] (mg/kg/day)	Duration of Treatment (weeks)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)

QUALITY OF EVIDENCE

Strengths of Study:	The dose of chloroethene was determined following gastrointestinal digestion of PVC-containing diet. Treatment was for the lifetime of the rats. Several dose levels were administered. A large number of rats of both sexes were used in each group.
Weakness of Study:	No control group for rats treated by gavage was included
Overall Adequacy:	Adequate

---

[a] Source: Feron et al., 1981

[b] Duration of study was for 143 weeks

[c] Purity of compound was not reported

[d] Dosage given 5 days/week

NA = Not applicable

TABLE 9-13

Bioassay Data for Humans Occupationally Exposed to Chloroetnene[a,b]

Size of Exposed Population	Size of Control Population	Sex	Target Organ	Tumor Type	Number of Cases Observed	Number of Cases Expected	Relative Risk
161	161	M	liver and biliary tract	cancer	8	0.7	11.4
			brain	cancer	5	1.2	4.2
			lung	cancer	13	7.9	1.6
			digestive	cancer	13	8.3	1.6
			lymphatic and hematopoietic system	cancer	5	3.4	1.5

QUALITY OF EVIDENCE

Strengths of Study:	Deaths in a chloroethene-exposed population were compared with a comparable age/time/cause-specific reference population. The incidence of several causes of death were examined.
Weakness of Study:	The levels of exposure and duration of exposure are not reported. No statistics are reported.
Overall Adequacy:	Adequate

---

[a] Source: Monson et al., 1974

[b] Level and duration of exposure not reported

TABLE 9-14

Bioassay Data for Humans Occupationally Exposed to Chloroethene[a,b]

Size of Exposed Population	Size of Control Population	Sex	Duration of Exposure	Target Organ	Tumor Type	Number of Cases Observed[c]	Number of Cases Expected	Relative Risk (p value)
1287	U.S. death rates	M,F	$\geq$5 years	liver and biliary tract	cancer	7	0.4	17.5 ($p<0.01$)
				brain and CNS	cancer	3	0.6	5.0 ($p<0.05$)
				lymphatic and hematopoietic	cancer	3	1.7	1.8 (NS)
				respiratory system	cancer	11	5.7	1.9 ($p<0.05$)

QUALITY OF EVIDENCE

Strengths of Study: Tumor incidences were analyzed on the basis of latency period. Statistical analyses of different types of cancer compared to expected values were performed. The study was of workers with $\geq$5 years exposure.

Weakness of Study: Levels of exposure were not available.

Overall Adequacy: Adequate

---

[a] Source: Waxweiler et al., 1976

[b] Level of exposure not reported

[c] Incidence of tumors after 15-year latency

NS = Not significant

TABLE 9-15

Bioassay Data for Humans Occupationally Exposed to Chloroethene*

Size of Exposed Population	Size of Control Population	Sex	Level of Exposure	Duration of Exposure	Target Organ	Tumor Type	Number of Cases Observed	Number of Cases Expected	Relative Risk (p value)
750	1969 Swedish population	M	periodically up to 15,000 ppm	>10 years	liver/pancreas	cancer	4	0.68	5.8 ($p<0.005$)
				<1 to >10 years	brain	cancer	2	0.33	6.1 ($p<0.043$)
				<1 to >10 years	lung	cancer	3	1.78	1.7 ($p<0.26$)

QUALITY OF EVIDENCE

Strengths of Study: The exposed population was compared to the Swedish population. The incidence of liver tumors was reported based on lengths of exposure. Statistics were compiled to show significant increases in tumor incidences.

Weakness of Study: Specific levels of exposure are not reported. A relatively small number of cancer deaths was examined.

Overall Adequacy: Adequate

---

*Source: Byren et al., 1976

TABLE 9-16

Bioassay Data for Humans Exposed to Chloroethene*

Exposure Route	Size of Exposed Population	Size of Control Population	Sex	Level of Exposure (ppm)	Duration of Exposure	Target Organ	Tumor Type	Number of Cases Observed	Number of Cases Observed	Relative Risk
Dermal plus inhalation plus oral	7409	death rates for England and Wales	M	<25 to >200	6-20 years	liver	cancer	4	1.64	2.44

QUALITY OF EVIDENCE

Strengths of Study: Levels of exposure of workers were estimated from air-sample metering. Duration of exposure was reported. The exposed population was compared to death rates (based on age groups) of England and Wales.

Weakness of Study: Few deaths were reported. No statistics were reported.

Overall Adequacy: Limited

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*Source: Fox and Collier, 1977

TABLE 9-17

Bioassay Data for Humans Occupationally Exposed to Chloroethene[a,b]

Size of Exposed Population	Size of Control Population	Sex	Duration of Exposure	Target Organ	Tumor Type	Number of Cases Observed	Number of Cases Expected	Relative Risk (p value)
4524	Japanese mortality rates	M	>1 year	all sites	malignant neoplasm	37	26.94	1.37 ($p<0.05$)
				liver	cancer	6	2.54	2.36 ($p<0.05$)

QUALITY OF EVIDENCE

Strengths of Study: A large group of workers having at least 1 year of exposure and 10 years latency was studied. Death certificates were obtained for a majority of deceased employees.

Weakness of Study: Exposure levels were not determined. Limited data on diagnosis and cause of death available from death certificates prevented specific classification of cancer types.

Overall Adequacy: Adequate

Comments: Data were for PVC-workers. Non PVC-workers showed no increase in cancer deaths.

---

[a] Source: Nakamara, 1983

[b] Level of exposure not significant

TABLE 9-18

Bioassay Data for Humans Occupationally Exposed to Chloroethene[a]

Size of Exposed Population	Size of Control Population	Sex	Level of Exposure	Duration of Exposure	Target Organ	Tumor Type	Number of Cases Observed	Number of Cases Expected	Relative Risk
454	Norway Cancer Mortality Records	M	varies over years[b]	>1 year	all sites	cancer	23	20.2	1.1
					liver	angiosarcoma	1	NR	NA
					lung	cancer	5	2.8	1.8
					colon	cancer	3	1.4	2.1
					thyroid	cancer	2	0.16	12.5
					skin	melanoma	4	0.8	5.0

QUALITY OF EVIDENCE

Strengths of Study: The cohort consisted of workers exposed for at least 1 year having a minimum of 10 years latency. Exposure levels were estimated.

Weakness of Study: The small number of cancer deaths prevents a definitive conclusion.

Overall Adequacy: Adequate

---

[a] Source: Heldaas et al., 1984

[b] Estimated 2000 ppm in 1950-1954; 1000 ppm in 1955-1959; 500 ppm in 1960-1967; 100 ppm in 1968-1974

NA = Not applicable; NR = Not reported

Chloroethene has been shown to be carcinogenic in rats, mice and hamsters and is regarded as a human carcinogen according to the IARC criteria (IARC, 1974, 1979, 1982). Under U.S. EPA's proposed risk assessment guidelines for carcinogenicity (Federal Register, 1984) chloroethene is classified in Group A. This classification indicates that there is sufficient epidemiological evidence to support a causal association between exposure and human cancer. In a battery of carcinogenicity tests of chloroethene Maltoni et al. (1980, 1981, 1982) have reported an increased incidence of liver angiosarcoma, kidney nephroblastoma, lung and brain tumors among rats and mice treated by inhalation or orally and forestomach tumors in hamsters exposed by inhalation. Numerous other studies (Lee et al., 1978; Hong et al., 1981, MCA, 1980; Hehir et al., 1981; Suzuki, 1981, 1983; Drew et al., 1983) have confirmed the development of liver angiosarcoma following inhalation exposure to chloroethene. In addition to the gavage study by Maltoni (1977a), Feron et al. (1981) and Dow Chemical Company (1983) have reported a carcinogenic effect on the liver and lungs following oral ingestion of chloroethene.

The predisposition of chloroethene and PVC workers to angiosarcoma of the liver has been reported in several case reports and numerous epidemiological studies (IARC, 1974, 1979; Monson et al., 1974; Waxweiler et al., 1976; Byren et al., 1976; Fox and Collier, 1977; Nakamura, 1983; Heldaas et al., 1984). These data are sufficient to regard chloroethene as a human carcinogen (IARC group 1). In addition to liver cancer, exposure to chloroethene has been associated with an increased risk of lung, brain, hematopoietic and digestive tract cancers.

The potency factor (F-factor) for the carcinogenicity of chloroethene will be determined from the available animal studies since exposure data for humans are lacking. Data on the development of liver angiosarcoma among rats exposed by inhalation (see Table 9-6; Maltoni et al., 1981) could be used to determine a potency factor for exposure by this route (Table 9-19). The unadjusted $1/ED_{10}$ was calculated using the computerized multistage model, GLOBAL 82 (Howe and Crump, 1982). The corrected $1/ED_{10}$ (F factor) was calculated by multiplying the unadjusted value by the cube root of the ratio of the human body weight (70 kg) to the rat weight (0.35 kg). The F-factor for chloroethene based on the development of liver angiosarcoma was determined to be 1.6 $(mg/kg/day)^{-1}$.

The U.S. EPA (1984a) recently indicated that the Carcinogen Assessment Group estimated the risk of carcinogenicity of chloroethene following oral ingestion based on dose-response data reported by Feron et al. (1981) (Table 9-20). The total combined incidence of liver and lung tumors among female rats exposed through the diet was used to estimate risk. Using the combined incidence for estimating carcinogenic risk a potency factor of 15.0 was determined. This F-factor is greater than that derived from the inhalation exposure study, and is, therefore, a more conservative estimate of the carcinogenic potency of chloroethene but has been determined using the combined incidence of liver and lung tumors. Combining tumor incidences may over estimate carcinogenic potency if tumor incidence does not represent primary tumors only.

According to the Hazard Ranking Scheme for Reportable Quantities for Carcinogenic Potency (U.S. EPA, 1984c) a chemical with an F factor of 10-100 is placed in Potency Group 2; the IARC classification as a Group 1 compound and the classification of chloroethene in Potency Group 2 ranks chloroethene as being a high hazard for carcinogenicity.

TABLE 9-19

Derivation of Potency Factor (F)
Agent: Chloroethene

Reference:	Maltoni et al., 1981			
Exposure route:	inhalation			
Species:	rat			
Strain:	Sprague-Dawley			
Sex:	M,F			
Vehicle or physical state:	air/vapor			
Body weight:[a]	0.35 kg			
Duration of treatment:	365 days			
Duration of study:	up to 1029 days			
Lifespan of animal:[b]	up to 1029 days			
Target organ:	liver	liver	liver	liver
Tumor type:	angiosarcoma	angiosarcoma	angiosarcoma	angiosarcoma
Experimental doses/exposure (mg/m^3):[c]	0.0	25.6	63.9	28
Transformed doses (mg/kg/day):	0.0	0.344	0.860	1.719
Tumor incidence:	0/363	1/119	5/120	1/60
Unadjusted 1/ED_{10} (F factor):	0.2777778 (mg/kg/day)$^{-1}$			
1/ED_{10} (F factor):	1.6 (mg/kg/day)$^{-1}$			

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[a] Estimated

[b] Reported, based on duration of longest study

[c] GLOBAL 82 rejected the goodness of fit hypothesis for exposures >128 mg/m^3

TABLE 9-20

Derivation of Potency Factor (F)
Agent: Chloroethene

Reference:	Feron et al., 1981			
Exposure route:	oral			
Species:	rat			
Strain:	Wistar			
Sex:	F			
Vehicle or physical state:	chloroethene-fortified PVC powder in diet			
Body weight[a]:	0.25 kg			
Duration of treatment:	1001 days			
Duration of study:	1001 days			
Lifespan of animal[b]:	1001 days			
Target organ:	combined lung and liver			
Tumor type:	angiosarcoma, hepatocellular carcinoma or neoplastic nodule			
Experimental doses/exposure:	0.0 mg/kg/day	1.8 mg/kg/day	5.6 mg/kg/day	17.0 mg/kg/day[c]
Transformed doses (mg/kg/day):	0.0	1.8	5.6	17.0
Tumor incidence:	2/57	26/58	42/59	56/57
Unadjusted $1/ED_{10}$ (F factor):	0.436 $(mg/kg/day)^{-1}$			
$1/ED_{10}$ (F factor):	15.0			

[a] Assumed

[b] Reported

[c] The $1/ED_{10}$ is based on the data up to 5.6 mg/kg/day. The goodness of fit hypothesis was rejected when the high dose was included.

10. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1985. Threshold Limit Values for Chemical Substances in the Work Environment. Adopted by ACGIH for 1984-1985.

Anderson, D. and C.R. Richardson. 1981. Issues relevant to the assessment of chemically induced chromosome damage in vivo and their relationship to chemical mutagenesis. Mutat. Res. 90(3): 261-272.

Anderson, D., M.C.E. Hodge and I.F.H. Purchase. 1977. Dominant lethal studies with the halogenated olefins vinyl chloride and vinylidene dichloride in male CD-1 mice. Environ. Health Perspect. 21: 71-78.

Ando, M. and Y. Sayato. 1984. Studies on vinyl chloride migrating into drinking water from poly(vinyl chloride) pipe and reaction between vinyl chloride and chlorine. Water Res. 18(3): 315-318.

Andrews, A.W., E.S. Zawistowski and C.R. Valentine. 1976. A comparison of the mutagenic properties of vinyl chloride and methyl chloride. Mutat. Res. 40(3): 273-275.

Atkinson, R. and J.N. Pitts, Jr. 1977. Rate constants for the reaction of oxygen (3P) atoms with vinyl flouride, vinyl chloride, and vinyl bromide over the temperature range 298-442°K. J. Chem. Phys. 67: 2488-2491.

Aviado, D.M. and D.G. Smith. 1975. Toxicity of aerosol propellants in the respiratory and circulatory systems. VIII. Respiration and circulation in primates. Toxicology. 3(2): 241-252.

Banzer, J.D. 1979. The migration of vinyl chloride monomer from PVC pipe into water. J. Vinyl Technol. 1(3): 164-167.

Bartsch, H. and R. Montesano. 1975. Mutagenic and carcinogenic effects of vinyl chloride. Mutat. Res. 32: 93-114.

Bartsch, H. and R. Montesano. 1980. Prescreening of environmental and industrial chemicals in a series of short-term tests for the detection of potential carcinogens. Environ. Res. Programme. p. 269-273.

Bartsch, H., C. Malaveille and R. Montesano. 1975. Human, rat and mouse liver-mediated mutagenicity of vinyl chloride in S. typhimurium strains. Int. J. Cancer. 15(3): 429-437.

Bartsch, H., C. Malaveille, A. Barbin and G. Planche. 1979. Mutagenic and alkylating metabolites of halo-ethylenes, chlorobutadienes and dichlorobutenes produced by rodent or human liver tissues. Evidence for oxirane formation by P450-linked microsomal mono-oxygenases. Arch. Toxicol. 41(4): 249-277.

Basler, A. and G. Roehrborn. 1980. Vinyl chloride: An example for evaluating mutagenic effects in mammals in vivo after exposure to inhalation. Arch. Toxicol. 45(1): 1-7.

Bertram, C.G. 1977. Minimizing emissions from vinyl chloride plants. Environ. Sci. Technol. 11(9): 864-868.

Black, C.M., K.I. Welsh, A.E. Walker, et al. 1983. Genetic susceptibility to scleroderma-like syndrome induced by vinyl chloride. Lancet. 1: 53-55.

Bolt, H.M. and J.G. Filser. 1977. Irreversible binding of chlorinated ethylenes to macromolecules. Environ. Health Perspect. 21: 107-112.

Bolt, H.M., H. Kappus, A. Buchter and W. Bolt. 1976. Disposition of (1,2-^{14}C) vinyl chloride in the rat. Arch. Toxicol. 35: 153-162. (Cited in U.S. EPA, 1984a)

Bolt, H.M., R.J. Laib, H. Kappus and A. Buchter. 1977. Pharmacokinetics of vinyl chloride in the rat. Toxicology. 7(2): 179-188.

Bolt, H.M., R.J. Laib and G. Stoeckle. 1979. Formation of pre-neoplastic hepatocellular foci by vinyl bromide in newborn rats. Arch. Toxicol. 43(1): 83-84.

Bolt, H.M., J.G. Filser and A. Buchter. 1981. Inhalation pharmacokinetics based on gas uptake studies. III. A pharmacokinetic assessment in man of peak concentrations of vinyl chloride. Arch. Toxicol. 48(4): 213-228.

Bozzelli, J.W. and B.B. Kebbekus. 1979. Analysis of selected volatile organic substances in ambient air, final report Apr-Nov 1978. NJ Institute of Technology, Newark, NJ. 80 p.

Bozzelli, J.W. and B.B. Kebbekus and A. Greenburg. 1980. Analysis of selected toxic and carcinogenic substances in ambient air in New Jersey. State of New Jersey, Department of Environmental Protection.

Brown, E.R., T. Sinclair, L. Keith, et al. 1977. Chemical pollutants in relation to diseases in fish. Ann. N.Y. Acad. Sci. 298: 535-546.

Bruckmann, P. and W. Muelder. 1982. Organic trace substance content in landfill gases. Schriftenr. Landesanst. Immissionsschutz Landes Nordrhein-Westfalen, Essen. 55: 21-28.

Buchter, A., H.M. Bolt, H. Kappus and W. Bolt. 1977. Tissue distribution of 1,2-14C-vinyl chloride in the rat. Int. Arch. Occup. Environ. Health. 39(1): 27-32.

Buchter, A., J.G. Filser, H. Peter and H.M. Bolt. 1980. Pharmacokinetics of vinyl chloride in the rhesus monkey. Toxicol. Lett. 6(1): 33-36.

Burmaster, D.E. 1982. The new pollution-groundwater contamination. Environ. 24: 6-13, 33-36.

Byren, D., G. Engholm, A. Englund and P. Westerholm. 1976. Mortality and cancer morbidity in a group of Swedish VCM and PVC production workers. Environ. Health Perspect. 17: 167-170.

Callahan, M.A., M.W. Slimak, N.W. Gabel, et al. 1979. Water-related environmental fate of 129 priority pollutants. Volume II. Washington, DC. EPA-440/4-79-029B.

Carassiti, V., C. Chiorboli, C.A. Bignozzi, A. Ferri and A. Maldotti. 1978. Atmospheric photooxidation of vinyl chloride: A generalized treatment of the relative rates of product formation. Ann. Chim. (Rome), Volume Date 1977, 67(7-8): 499-512.

CMR (Chemical Marketing Reporter). 1983. Chemical Profile - Vinyl chloride. Chemical Marketing Reporter, June 20, 1983.

Code of Federal Regulations. 1981. OSHA Safety and Health Standards (29 CFR 1910.1017).

Cole, R.H., R.E. Frederick, R.P. Healy and R.G. Rolan. 1984. Preliminary findings of the priority pollutant monitoring project of the nationwide urban runoff program. J. Water Pollut. Control Fed. 56: 898-908.

Coniglio, W.A., K. Miller and D. Mackeever. 1980. The occurrence of volatile organics in drinking water. Criteria and Standards Division. Science and Technology Branch. Exposure Assessment Project.

Conolly, R.B. and R.J. Jaeger. 1977. Acute hepatotoxicity of ethylene and halogenated ethylenes after PCB pretreatment. Environ. Health Perspect. 21: 131-135.

Conolly, R.B. and R.J. Jaeger. 1979. Acute hepatoxicity of vinyl chloride and ethylene: Modification by trichloropropene oxide, diethylmaleate, and cysteine. Toxicol. Appl. Pharmacol. 50(3): 523-531.

Conolly, R.B., R.J. Jaeger and S. Szabo. 1978. Acute hepatotoxicity of ethylene, vinyl flouride, vinyl chloride, and vinyl bromide after Aroclor 1254 pretreatment. Exp. Mol. Pathol. 28(1): 25-33.

Cotti, G., L. Valgimigli, A. Mandrioli and C. Maltoni. 1983. Suitable models for long-term bioassays of therapeutic and toxic effects of anti-blastic drugs: Brain tumors of neuronal cells and primitive bipotential precursors produced in Sprague-Dawley rats by vinyl chloride. Dev. Oncol. 15: 376-378.

Cowfer, J.A. and A.J. Magistro. 1983. Vinyl polymers (vinyl chloride). In: Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed., Vol. 23, M. Grayson and D. Eckroth, Ed. John Wiley and Sons, Inc., New York. p. 865-885.

Cox, R.A., A.E.J. Eggleton and F.J. Sandalls. 1974. Photochemical reactivity of vinyl chloride. AERE-R7820. Aere Harwell, Oxfordshire, England. 16 p.

Creech, J.L. and M.N. Johnson. 1974. Angiosarcoma of the liver in the manufacture of polyvinyl chloride. J. Occup. Med. 16: 150-151.

Cupitt, L.T. 1980. Fate of Toxic and Hazardous Materials in the Air Environment. Environmental Sciences Research Laboratory, U.S. EPA, Research Triangle Park, NC. EPA-600/S3-80-084.

DeMeester, C., B. Duverger-Van, M. Lambotte-Vandepaer, M. Roberfroid, F. Poncelet and M. Mercier. 1980. Mutagenicity of vinyl chloride in the Ames test. Possible artifacts related to experimental conditions. Mutat. Res. 77(2): 175-179.

Destouet, J.M. and W.A. Murphy. 1983. Acquired acroosteolysis and acronecrosis. Arthritis Rheum. 26(9): 1150-1154.

Dietz, F.K., J.C. Ramsey and P.G. Watanabe. 1983. Relevance of experimental studies to human risk. Environ. Health Perspect. 52: 9-14.

Dilling, W.L. 1977. Interphase transfer processes. II. Evaporation rates of chloromethanes, ethanes, ethylenes, propanes and propylenes from dilute aqueous solutions. Comparisons with theoretical predictions. Environ. Sci. Technol. 11: 405-409.

Dilling, W.L., N.B. Tefertiller and G.J. Kallos. 1975. Evaporation rates and reactivities of methylene chloride, chloroform, 1,1,1-trichloroethane, trichloroethylene, tetrachloroethylene and other chlorinated compounds in dilute aqueous solutions. Environ. Sci. Technol. 9: 833-838.

Dilling, W.L., C.J. Bredeqeg and N.B. Tefertiller. 1976. Organic photochemistry. XIII. Simulated atmospheric photodecomposition rates of methylene chloride, 1,1,1-trichloroethane, trichloroethylene, tetrachloroethylene and other chlorinated compounds in dilute aqueous solutions. Environ. Sci. Technol. 10: 351-356.

Doss, M., C.E. Lange and G. Veldtman. 1984. Vinyl chloride-induced hepatic coproporhyrinuria with transition to chronic hepatic porphyria. Klin. Wochensche. 62: 175-178.

Dow Chemical Company. 1983. Submission of information on vinyl chloride with enclosures and EPA Response Dated 10/11/83. FYI-OTS-0983-0265IN.

Dow Chemical Company. 1984. Summary of Report on Lifespan Oral Carcinogenicity Study of Vinyl Chloride in Rats. FYI-OTS-1084-0353IN. FYI-AX-1084-0353SU.

Drevon, C. and T. Kuroki. 1979. Mutagenicity of vinyl chloride, vinylidene chloride and chloroprene in V79 Chinese hamster cells. Mutat. Res. 67(2): 173-182.

Drew, R.T., C. Harper, B.N. Gupta and F.A. Talley. 1975. Effects of vinyl chloride exposures to rats pretreated with phenobarbital. Environ. Health Perspect. 11: 235-242.

Drew, R.T., G.A. Boorman, J.K. Haseman, E.E. McConnell, W.M. Busey and J.A. Moore. 1983. The effect of age and exposure duration on cancer induction by a known carcinogen in rats, mice, and hamsters. Toxicol. Appl. Pharmacol. 68(1): 120-130.

Drozdowicz, B.Z. and P.C. Huang. 1977. Lack of mutagenicity of vinyl chloride in two strains of Neurospora crassa. Mutat. Res. 48(1): 43-50.

Du, J.T., J.P. Sandoz, M.T. Tseng and C.H. Tamburro. 1979. Biochemical alterations in livers of rats exposed to vinyl chloride. J. Toxicol. Environ. Health. 5(6): 1119-1132.

Duprat, P., J.P. Fabry, D. Gradiski and J.L. Magadur. 1977. Metabolic approach to industrial poisoning: Blood kinetics and distribution of 14C-vinyl chloride monomer (V.C.M.). Acta. Pharmacol. Toxicol. Suppl. (Kbh) 41(1): 142-143. (Cited in U.S. EPA, 1984a)

Duverger, M., M. Lambotte, E. Malvoisin, D. DeMeester, F. Poncelet and M. Mercier. 1981. Metabolic activation and mutagenicity of 4 vinyl monomers (vinyl chloride, styrene, acrylonitrile, butadiene). Toxicol. Eur. Res. 3(3): 131-140.

Dyksen, J.E. and A.F. Hess, III. 1982. Alternatives for controlling organics in ground water supplies. J. Am. Water Works Assoc. 74: 394-403.

Edmonds, L.D., C.E. Anderson, J.W. Flynt, Jr. and L.M. James. 1978. Congenital central nervous system malformations and vinyl chloride monomer exposure: A community study. Teratology. 17: 137-142.

Elmore, J.D., J.L. Wong, A.D. Laumbach and U.N. Streips. 1976. Vinyl chloride mutagenicity via the metabolites chlorooxirane and chloroacetaldehyde monomer hydrate. Biochim. Biophys. Acta. 442(3): 405-419.

Evans, D.M., W.J. Williams and I.T. Kung. 1983. Angiosarcoma and hepatocellular carcinoma in vinyl chloride workers. Histopathology. 7(3): 377-388.

Fabricant, J.D. and M.S. Legator. 1981. Mutagenicity studies of vinyl chloride. Environ. Health Perspect. 41: 189-193.

Federal Register. 1974. Standard for Exposure to Vinyl Chloride. 39(194)FR: 35890-35898.

Federal Register. 1980. Guidelines and Methodology for the Preparation of Health Effects Assessment Chapters of the Ambient Water Quality Criteria Documents. 45 FR 79318.

Federal Register. 1984. Proposed Guidelines for Carcinogen Risk Assessment. 47 FR 46294-46301.

Feron, V.J. and R. Kroes. 1979. One-year time-sequence inhalation toxicity study of vinyl chloride in rats. II. Morphological changes in the respiratory tract, ceruminous glands, brain, kidneys, heart and spleen. Toxicology. 13(2): 131-141.

Feron, V.J., A.J. Speek, M.I. Willems, D. VanBattum and A.P. Groot. 1975. Observations on the oral administration and toxicity of vinyl chloride in rats. Food Cosmet. Toxicol. 13(6): 633-638.

Feron, V.J., A. Kruysse and H.P. Til. 1979a. One-year time-sequence inhalation toxicity study of vinyl chloride in rats. I. Growth, mortality, hematology, clinical chemistry and organ weights. Toxicology. 13(1): 25-28.

Feron, V.J., B.J. Spit, H.R. Immel and R. Kroes. 1979b. One-year time-sequence inhalation toxicity study of vinyl chloride in rats. III. Morphological changes in the liver. Toxicology. 13(2): 143-154.

Feron, V.J., C.F.M. Hendriksen, A.J. Speek, H.P. Til and B.J. Spit. 1981. Lifespan oral toxicity study of vinyl chloride in rats. Food Cosmet. Toxicol. 19(3): 317-333.

Filser, J.G. and H.M. Bolt. 1979. Pharmacokinetics of halogenated ethylenes in rats. Arch. Toxicol. 42(2): 123-136.

Fishbein, L. 1979. Potential halogenated industrial carcinogenic and mutagenic chemicals. I. Halogenated unsaturated hydrocarbons. Sci. Total Environ. 11: 111-161.

Fleig, I. and A.M. Thiess. 1978. Mutagenicity of vinyl chloride. External chromosome studies on persons with and without VC illness and on VC exposed animals. J. Occup. Med. 20(8): 557-561.

Fox, A.J. and P.F. Collier. 1977. Mortality experience of workers exposed to vinyl chloride monomer in the manufacture of polyvinyl chloride in Great Britain. Br. J. Ind. Med. 34: 1-10.

Fujimoto, T., A.M. Rennert and M.H.J. Wijnen. 1970. Primary steps in the photolysis of vinyl chloride. Ber. Bunsenges. Phys. Chem. 74: 282-286.

Garro, A.J., J.B. Guttenplan and P. Milvy. 1976. Vinyl chloride dependent mutagensis: Effects of liver extracts and free radicals. Mutat. Res. 38(2): 81-88.

Gay, B.W., Jr. and R.C. Noonan. 1975. Ambient air measurements of vinyl chloride in the Niagara Falls area; environmental monitoring series. National Environmental Research Center, Research Triangle Park, NC. EPA-650/4-75-020.

Gay, B.W., Jr., P.L. Hanst, J.J. Bufalini and R.C. Noonan. 1976. Atmospheric oxidation of chlorinated ethylenes. Environ. Sci. Technol. 10: 58-66.

Gehring, P.J., P.G. Watanabe and C.N. Park. 1978. Resolution of dose-response toxicity data for chemicals requiring metabolic activation: Example-vinyl chloride. Toxicol. Appl. Pharmacol. 44(3): 581-591.

Gilbert, S.G., J. Miltz and J.R. Giacin. 1980. Transport considerations of potential migrants from food packaging materials. J. Food Process. Preserv. 4(1-2): 27-49.

Gordon, S.J. and S.A. Meeks. 1977. A study of gaseous pollutants in the Houston, Texas area. Aiche Symp. Ser. 73: 84-94.

Graedel, T.E. 1978. Chemical compounds in the atmosphere. Academic Press, New York, NY. p. 1148.

Green, T. and D.E. Hathway. 1975. Biological fate in rats of vinyl chloride in relation to its oncogenicity. Chem.-Biol. Interact. 11(6): 545-562.

Greim, H., G. Bonse, Z. Radwan, D. Reichert and D. Henschler. 1975. Mutagenicity in vitro and potential carcinogenicity of chlorinated ethylenes as a function of metabolic oxirane formation. Biochem. Pharmacol. 24(21): 2013-2017.

Greim, H., D. Bimboes, G. Egert, W. Goeggelmann and M. Kraemer. 1977. Mutagenicity and chromosomal aberrations as an analytical tool for in vitro detection of mammalian enzyme-mediated formation of reactive metabolites. Arch. Toxicol. 39(1): 159-169.

Grimsrud, E.P. and R.A. Rasmussen. 1975. Survey and analysis of halocarbons in the atmosphere by gas chromatography-mass spectrometry. Atmos. Environ. 9: 1014-1017.

Guengerich, F.P. and P.G. Watanabe. 1979. Metabolism of ^{14}C- and ^{36}Cl-labeled vinyl chloride *in vivo* and *in vitro*. Biochem. Pharmacol. 28(5): 589-596.

Guengerich, F.P., P.S. Mason, W.T. Stott, T.R. Fox and P.G. Watanabe. 1981. Roles of 2-haloethylene oxides and 2-haloacetaldehydes derived from vinyl bromide and vinyl chloride in irreversible binding to protein and DNA. Cancer Research. 41(11): 4391-4398.

Guesten, H., W.G. Filby and S. Schoof. 1981. Prediction of hydroxyl radical reaction rates with organic compounds in the gas phase. Atmos. Environ. 15: 1763-1765.

Gwinner, L.M., R.J. Laib, J.G. Filser and H.M. Bolt. 1983. Evidence of chloroethylene oxide being the reactive metabolite of vinyl chloride towards DNA: Comparative studies with 2,2'-dichlorodiethyl ether. Carcinogenesis. 4(11): 1483-1486.

Hansteen, I.L., L. Hillestad, E. Thiis-Evensen and S.S. Heldaas. 1978. Effects of vinyl chloride in man. A cytogenetic follow-up study. Mutat. Res. 51(2): 271-278.

Harkov, R., B. Kebbekus, J.W. Bozzelli and P.J. Lioy. 1983. Measurement of selected volatile organic compounds at three locations in New Jersey during the summer season. J. Air. Pollut. Control Assoc. 33: 1177-1183.

Harkov, R., B. Kebbekus, J.W. Bozzelli, P.J. Lioy and J. Daisey. 1984. Comparison of selected volatile organic compounds during the summer and winter at urban sites in New Jersey. Sci. Total Environ. 38: 259-274.

Hathway, D.E. 1977. Comparative mammalian metabolism of vinyl chloride and vinylidene chloride in relation to oncogenic potential. Environ. Health Perspect. 21: 55-59.

Hedley, W.H., J.T. Cheng, R.J. McCormick and W.A. Lewis. 1976. Sampling of automobile interiors for vinyl chloride monomer. NTIS PB-258648, 42 p.

Hefner, R.E., Jr., P.G. Watanabe and P.J. Gehring. 1975a. Percutaneous absorption of vinyl chloride. Toxicol. Appl. Pharmacol. 34(3): 529-532.

Hefner, R.E., Jr., P.G. Watanabe and P.J. Gehring. 1975b. Preliminary studies of the fate of inhaled vinyl chloride monomer in rats. Ann. NY Acad. Sci. 246: 135.

Hefner, R.E., Jr., P.G. Watanabe and P.J. Gehring. 1975c. Fate of inhaled vinyl chloride monomer in rats. Environ. Health Perspect. 11: 85-95.

Hehir, R.M., B.P. McNamara, J. McLaughlin, Jr., D.A. Willigan, G. Bierbower and J.F. Hardisty. 1981. Cancer induction following single and multiple exposures to a constant amount of vinyl chloride monomer. Environ. Health Perspect. 41: 63-72.

Heldaas, S.S., S.L. Langard and A. Andersen. 1984. Incidence of cancer among vinyl chloride and polyvinyl chloride workers. Br. J. Ind. Med. 41(1): 25-30.

Helfgott, T.B., F.L. Hart and R.G. Bedard. 1977. An index of refractory organics. U.S. EPA, ADA, OK. EPA-600/2-77-174. p. 1309.

Henschler, D. and G. Bonse. 1977. Metabolic activation of chlorinated ethylenes: Dependence of mutagenic effect on electrophilic reactivity of the metabolically formed epoxides. Arch. Toxicol. 39(1): 7-12.

Hill, J., IV, H.P. Kollig, D.F. Paris, N.L. Wolfe and R.G. Zepp. 1976. Dynamic behavior of vinyl chloride in aquatic ecosystems. U.S. EPA, Athens, GA. EPA-600/3-76-001.

Himeno, S., H. Okuda and T. Suzuki. 1983. Lack of dominant lethal effects in male CD-1 mice after short-term and long-term exposures to vinyl chloride monomer. Toxicol. Lett. 16(1-2): 47-53. (CA 98:174531)

Hong, C.B., J.M. Winston, L.P. Thornburg, C.C. Lee and J.S. Woods. 1981. Follow-up study on the carcinogenicity of vinyl chloride and vinylidene chloride in rats and mice: Tumor incidence and mortality subsequent to exposure. J. Toxicol. Environ. Health. 7: 909-924.

Hopkins, J. 1980. Vinyl chloride. Part 5. Mutagenicity in man. Food Cosmet. Toxicol. 18(2): 200-201.

Horvath, A.L. 1982. Halogenated Hydrocarbons. Solubility Miscibility with Water. Marcel Dekker, Inc., New York. p. 494, 692-694.

Howard, C.J. 1976. Rate constants for the gas-phase reactions of hydroxyl radicals with ethylene and halogenated ethylene compounds. J. Chem. Phys. 65: 4771-4777.

Howe, R.B. and K.S. Crump. 1982. GLOBAL 82. A computer program to extrapolate quantal animal toxicity data to low doses. Prepared under Contract 41USC252C3. Office of Carcinogen Standards, OSHA, U.S. Dept. of Labor.

Hultmark, D., K. Sundh, L. Johansson and E. Arrhenius. 1979. Ethanol inhibition of vinyl chloride metabolism in isolated rat hepatocytes. Chem.-Biol. Interact. 25(1): 1-6.

IARC (International Agency for Research on Cancer). 1974. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. WHO, Lyon, France. Vol. 7.

IARC (International Agency for Research on Cancer). 1979. Some monomers, plastics and synthetic elastomers, and acrolein. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. WHO, Lyon, France. Vol. 9, p. 377-438.

IARC (International Agency for Research on Cancer). 1982. IARC monographs on the evaluation of carcinogenic risk of chemicals to man. Chemicals, industrial processes and industries associated with cancer in humans. Suppl. 4: 260-262. Lyon, France.

Infante, P.F. 1981. Observations of the site-specific carcinogenicity of vinyl chloride to humans. Environ. Health Perspect. 41: 89-94.

Jaeger, R.J., E.S. Reynolds, R.B. Conolly, M.T. Moslen, S. Szabo and S.D. Murphy. 1974. Acute hepatic injury by vinyl chloride in rat pretreated with phenobarbital. Nature (London). 252(5485): 724-726.

Jaeger, R.J., R.B. Conolly and S.D. Murphy. 1975. Short-term inhalation toxicity of halogenated hydrocarbons. Effects on fasting rats. Arch. Environ. Health. 30(1): 26-31.

Jaeger, R.J., S.D. Murphy, E.S. Reynolds, S. Szabo and M.T. Moslen. 1977. Chemical modification of acute hepatotoxicity of vinyl chloride monomer in rats. Toxicol. Appl. Pharmacol. 41(3): 597-607.

Jedrychowski, R.A., J.A. Sokal and J. Chmielnicka. 1984. Influence of exposure mode on vinyl chloride action. Arch. Toxicol. 55(3): 195-198.

Jenssen, D. and C. Ramel. 1980. The micronucleus test as part of a short-term mutagenicity test program for the prediction of carcinogenicity evaluated by 143 agents tested. Mutat. Res. 75: 191-202.

John, J.A., F.A. Smith, B.K.J. Leong and B.A. Schwetz. 1977. The effects of maternally inhaled vinyl chloride on embryonal and fetal development in mice, rats, and rabbits. Toxicol. Appl. Pharmacol. 39(3): 497-513.

John, J.A., F.A. Smith and B.A. Schwetz. 1981. Vinyl chloride: Inhalation teratology study in mice, rats and rabbits. Environ. Health Perspect. 41: 171-177.

Jury, W.A., W.F. Spencer and W.J. Farmer. 1984. Behavior assessment model for trace organics in soil. III. Applicaton of screening model. J. Environ. Qual. 13: 573-579.

Kagiya, T., K. Takemoto and Y. Uyama. 1975. Photooxidative decomposition of vinyl chloride in the air. Nippon Kagaku Kaishi. 11: 1922-1925.

Kalmaz, E.E. and G.D. Kalmaz. 1984. Carcinogenicity and epdiemiological profile analysis of vinyl chloride and polyvinyl chloride. Regul. Toxicol. Pharmacol. 4(1): 13-27.

Kanno, S., K. Nojima, K. Takahashi, H. Iseki, S. Takamori and K. Takamatsu. 1977. Studies on the photochemistry of aliphatic halogenated hydrocarbons. II. Photochemical decomposition of vinyl chloride and ethyl chloride in the presence of nitrogen oxides in air. Chemosphere. 6: 509-514.

Kappus, H., H.M. Bolt, A. Buchter and W. Bolt. 1976. Liver microsomal uptake of carbon-14-labeled vinyl chloride and transformation to protein alkylating metabolites in vitro. Toxicol. Appl. Pharmacol. 37(3): 461-471.

Kenaga, E.E. and C.A.I. Goring. 1978. Relationship Between Water Solubility, Soil-Sorption, Octanol-Water Paritioning, and Bioconcentration of Chemicals in Biota. Prepublication copy of paper dated October 13, 1978 given at the Third Aquatic Toxicology Symposium, American Society for Testing and Materials, New Orleans, LA. October 17-18, 1978.

Keplinger, M.L., et al. 1975. Interim results of exposure of rats, hamsters, and mice to vinyl chloride. Ann. NY Acad. Sci. 246: 219.

Krahn, D.F. 1979. Utilization of the CHO/HGPRT system: Metabolic activation and method for testing gases. Banbury Rep. 2: 251-261. (CA 92:122911)

Krahn, D.F., F.C. Barsky and K.T. McCooey. 1982. CHO/HGPRT mutation assay: Evaluation of gases and volatile liquids. Environ. Sci. Res. 25: 91-103. (CA 97:34540)

Krajewski, J., M. Dobecki and J. Gromiec. 1980. Retention of vinyl chloride in the human lung. Br. J. Ind. Med. 37(4): 373-374.

Kucerova, M., Z. Polivkova and J. Batora. 1979. Comparative evaluation of the frequency of chromosomal aberrations and the sister-chromatid exchange (SCE) numbers in peripheral lymphocytes of workers occupationally exposed to vinyl chloride monomer. Mutat. Res. 67(1): 97-100.

Langauer-Lewowicka, H., H. Kurzbauer, Z. Byczkowska and T. Wocka-Marek. 1983. Vinyl chloride disease-neurological disturbances. Int. Arch. Occup. Environ. Health. 52(2): 151-157. (CA 99:145391)

Lee, C.C., J.C. Bhandari, J.M. Winston, et al. 1977a. Inhalation toxicity of vinyl chloride and vinylidene chloride. Environ. Health Perspect. 21: 25-32.

Lee, F.I., D.S. Harry, W.G.F. Adams and M. Litchfield. 1977b. Screening for liver disease in vinyl chloride workers. Br. J. Ind. Med. 34(2): 142-147.

Lee, C.C., J.C. Bhandari, J.M. Winston, W.B. House, R.L. Dixon and J.S. Woods. 1978. Carcinogenicity of vinyl chloride and vinylidene chloride. J. Toxicol. Environ. Health. 4: 15-30.

Lilis, R., H. Anderson, W.J. Nicholson, S. Daum, A.S. Fischbein and I.J. Selikoff. 1975. Prevalence of disease among vinyl chloride and polyvinyl chloride workers. Ann. NY Acad. Sci. 246: 22-41.

Lillian, D., H.B. Singh, A. Appleby, et al. 1975. Atmospheric fates of halogenated compounds. Environ. Sci. Technol. 9: 1042-1048.

Lloyd, M.H., S. Gauld, L. Copland and C.A. Soutar. 1984. Epidemiological study of the lung function of workers at a factory manufacturing polyvinylchloride. Br. J. Ind. Med. 41(3): 328-333.

Loprieno, N. 1977. The use of yeast cells in the mutagenic analysis of chemical carcinogens. Colloq. Int. C.N.R.S. 256: 315-331.

Lu, P.Y., R.L. Metcalf, N. Plummer and D. Mandel. 1977. The environmental fate of three carcinogens: Benzo(a)pyrene, benzidine and vinyl chloride evaluated in laboratory model ecosystems. Arch. Environ. Contam. Toxicol. 6: 129-142.

Lyman, W.J., W.F. Reehe and D.H. Rosenblatt. 1982. Handbook of Chemical Property Estimation Methods. Environmental Behavior of Organic Compounds. McGraw-Hill Book Co., New York. 960 p.

Mabey, W.R., J.H. Smith, R.T. Podoll, et al. 1981. Aquatic fate process data for organic priority pollutants. U.S EPA, Monitoring and Data Support Division (WH 553), Office of Water Regulations and Standards, Washington, DC. EPA 440/4-81-014.

Magnusson, J. and C. Ramel. 1978. Mutagenic effects of vinyl chloride on Drosophila melanogaster with and without pretreatment with sodium phenobarbiturate. Mutat. Res. 57(3): 307-312.

Malaveille, C., H. Bartsch, A. Barbin, et al. 1975. Mutagenicity of vinyl chloride, chloroethyleneoxide, chloroacetaldehyde, and chlorethanol. Biochem. Biophys. Res. Commun. 63(2): 363-370.

Maltoni, C. 1977a. Vinyl chloride carcinogenicity: An experimental model for carcinogenesis studies. In: Origins of Human Cancer, Book A, H.H. Hiatt, J.D. Watson and J.A. Winsten, Ed. Cold Spring Harbor Laboratory, Cold Spring Harbor, NY. p. 119-146.

Maltoni, C. 1977b. Recent findings on the carcinogenicity of chlorinated olefins. Environ. Health Perspect. 21: 1-5.

Maltoni, C. and G. Lefemine. 1974. Carcinogenicity bioassays of vinyl chloride. I. Research plan and early results. Environ. Res. 7(3): 387-405.

Maltoni, C. and G. Lefemine. 1975. Carcinogenicity bioassays of vinyl chloride. Current results. Ann. NY Acad. Sci. 246: 195-218.

Maltoni, C., G. Lefemine, A. Ciliberti, G. Cotti and D. Carretti. 1980. Vinyl chloride carcinogenicity bioassays (BT project) as an experimental model for risk identification and assessment in environmental and occupational carcinogenesis. Epidemiol. Anim. Epidemiol. Hum.: Cas Chlorure Vinyle Monomere, (Reun. Club Cancerog. Chim.), 20th, Meeting Date 1979, 11-112. Publ. Essent., Paris, France.

Maltoni, C., G. Lefemine, A. Ciliberti, G. Cotti and D. Carretti. 1981. Carcinogenicity bioassays of vinyl chloride monomer: A model of risk assessment on an experimental basis. Environ. Health Perspect. 41: 3-29.

Maltoni, C., G. Lefemine, A. Ciliberti, G. Cotti and D. Carretti. 1982. Vinyl chloride: A model carcinogen for risk assessment. Environ. Sci. Res. 25: 329-344.

Maltoni, G. Cotti, L. Valgimigli and A. Mandrioli. 1983. Suitable models for long-term bioassays of the therapeutic and toxic effects of antiblastic drugs: Liver angiosarcomas produced in Sprague-Dawley rats by vinyl chloride. Dev. Oncol. 15: 339-341.

MCA (Manufacturing Chemists Association). 1980. Letter regarding the study and report of effects of vinyl chloride. FYI-OTS-0480-0065.

McConnell, G., D.M. Ferguson and C.R. Pearson. 1975. Chlorinated hydrocarbons and the environment. Endeavour. 34: 13-18.

McMurry, J.R. and J. Tarr. 1978. Vinyl chloride in Texas' ambient air. Proc. Annu. Tech. Meet. - Inst. Environ. Sci. 24: 149-153.

Mirkova, E., A. Mihailova and M. Nosko. 1978. Embryotoxic and teratogenic effects of vinyl chloride. Khig. Zdraveopaz. 21(5): 440-443. (CA 90:98232)

Monson, R.R., J.M. Peters and M.N. Johnson. 1974. Proportional mortality among vinyl-chloride workers. Lancet. 2: 397-398.

Muller, J.P.H. and F. Korte. 1977. Contributions to ecological chemistry CXXXVI. Short report on the unsensitized photooxidation of chloroethylenes. Chemosphere. 6: 341-346.

Nakamura, K. 1983. A mortality study of vinyl chloride workers in Japan. Sangyo Ika Daigaku Zasshi. 5: 49-57.

Nakamura, H. and S. Mimura. 1977. Hygienic studies on materials for water supplies. I. Residual vinyl chloride monomer in commercial PVC pipe and water extractability of residual vinyl chloride monomer. Tokyo-toritsu Eisei Kenkyusho Kenkyu Nempo. 28-1: 264-268. [CA 91(8):62157u]

NIOSH (National Institute for Occupational Safety and Health). 1975. Recommended standard for occupatonal exposure to vinyl chloride. NTIS PB-246-691.

Pellizzari, E.D. 1977. The measurement of carcinogenic vapors in ambient atmospheres. U.S. EPA, Gulf Breeze, FL. EPA 600/7-77-055.

Pellizzari, E.D. 1978. Quantification of chlorinated hydrocarbons in previously collected air samples. Gov. Rep. Announce. Index. 79: 68. EPA 450/3-78-112.

Pellizzari, E.D., M.D. Erickson and R.A. Zweidinger. 1979. Formulation of preliminary assessment of halogenated organic compounds in man and environmental media. U.S. EPA, Research Triangle Park, NC. 469 p. EPA 560/13-79-006.

Perry, R.A., R. Atkinson and J.N. Pitts, Jr. 1977. Rate constants for the reaction of hydroxyl radicals with vinyl fluoride, vinyl chloride, and vinyl bromide over the temperature range 229-426°K. J. Chem. Phys. 67: 458-462.

Pessayre, D., J.C. Wandscheer, V. Descatoire, J.Y. Artigou and J.P. Benhamou. 1979a. Formation and inactivation of a chemically reactive metabolite of vinyl chloride. Toxicol. Appl. Pharmacol. 49(3): 505-515.

Pessayre, D., J.C. Wandscheer, V. Descatoire, A. Dolder and J.P. Benhamou. 1979b. Effects of inducers on the in vivo covalent binding of a vinyl chloride metabolite to liver fractions. Biochem. Pharmacol. 28(24): 3667-3668.

Pessayre, D., J.C. Wandscheer, V. Descatoire, A. Dolder, C. Degott and J.P. Benhamou. 1980. Cumulative effects of repeated doses of compounds transformed into reactive metabolites. Biochem. Pharmacol. 29(7): 1041-1047.

Peter, S. and G. Ungvary. 1980. Lack of mutagenic effect of vinyl chloride monomer in the mammalian spot test. Mutat. Res. 77(2): 193-196.

Pfaudler Co. 1984. Results of analytical data with attached tables. FYI-OTS-0185-0375.

Poncelet, F., C. DeMeester, M. Duverger-Van Bogaert, M. Lambotte-Vandepaer, M. Roberfroid and M. Mercier. 1980. Influence of experimental factors on the mutagenicity of vinylic monomers. Arch. Toxicol. Suppl. 4: 63-66.

Rannug, U., A. Johansson, C. Ramel and C.A. Wachtmeister. 1974. Mutagenicity of vinyl chloride after metabolic activation. Ambio. 3(5): 194-197.

Reynolds, E.S., M.T. Moslen, S. Szabo, R.J. Jaeger and S.D. Murphy. 1975. Hepatotoxicity of vinyl chloride and 1,1-dichloriethylene. Role of mixed function oxidase system. Am. J. Pathol. 81(1): 219-236.

Rice, J.M. 1981. Prenatal susceptibility to carcinogenesis by xenobiotic substances including vinyl chloride. Environ. Health Perspect. 41: 179-188.

Richardson, C.R., J.A. Styles and I.P. Bennett. 1983. Activity of vinyl chloride monomer in the mouse micronucleus assay. Mutat. Res. 122(2): 139-142.

Sabadie, N., C. Malaveille, A.M. Camus and H. Bartsch. 1980. Comparison of the hydroxylation of benzo(a)pyrene with the metabolism of vinyl chloride, N-nitrosomorpholine, and N-nitroso-N'-methylpiperazine to mutagens by human and rat liver microsomal fractions. Cancer Res. 40(1): 119-126.

Sabljic, A. 1984. Prediction of the nature and strength of soil sorption of organic pollutants by molecular topology. J. Agric. Food Chem. 32: 243-246.

Sakabe, H. 1975. Bone lesions among polyvinyl chloride production workers in Japan. Ann. NY Acad. Sci. 246: 78.

Sal'nikova, L.S. and I.A. Kitsovskaya. 1980. Effect of vinyl chloride on embryogenesis of rats. Gig. Tr. Prof. Zabol. (3): 46-47. (CA 92:192236)

Samoiloff, M.R., S. Schulz, Y. Jordan, K. Denich and E. Arnott. 1980. A rapid simple long-term toxicity assay for aquatic contaminants using the nematode Panagrellus redivivus. Can. J. Fish. Aquat. Sci. 37(7): 1164-1174.

Sanhueza, A. and J. Heicklen. 1975. Oxidation of chloroethylene. J. Phys. Chem. 79: 677-681.

Scherb, K. 1978. Studies on the evaporation of several low molecular weight chlorinated hydrocarbons form a flowing channels. Muench. Beitr. Abwasser-, Fisch.-Flussbiol. 30: 234-248.

Shahin, M.M. 1976. The non-mutagenicity and recombinogenicity of vinyl chloride in the absence of metabolic activation. Mutat. Res. 40(3): 269-272.

Simmon, V.F. 1978. Structural correlations of carcinogenic and mutagenic alkyl halides. DHEW Publ. (FDA) (US), Volume Date 1977, FDA 78-1046, Struct. Correl. Carcinog. Mutagen., 163-171.

Sokal, J.A., B. Baranski, J. Majka, et al. 1980. Experimental studies on the chronic toxic effects of vinyl chloride in rats. J. Hyg. Epidemiol. Microbiol. Immunol. 24(3): 285-294.

Spirtas, R., G. Beebe, P. Baxter, et al. 1983. Angiosarcoma as a model for comparative carcinogenesis (letter). Lancet. 2(8347): 456.

SRI (Stanford Research Institute) International. 1984. 1984 Directory of Chemical Producers: United States of America. SRI International, Menlo Park, CA.

Styles, J.A. 1977. A method for detecting carcinogenic organic chemicals using mammalian cells in culture. Br. J. Cancer. 36(5): 558-563.

Suzuki, Y. 1980. Nonneoplastic effects of vinyl chloride in mouse lung. Environ. Res. 21(1): 235-253.

Suzuki, Y. 1981. Neoplastic and nonneoplastic effects of vinyl chloride in mouse lung. Environ. Health Perspect. 41: 31-52.

Suzuki, Y. 1983. Neoplastic effect of vinyl chloride in mouse lung--lower doses and short-term exposure. Environ. Res. 32(1): 91-103.

Tamburro, C.H. 1984. Relationship of vinyl monomers and liver cancers: Angiosarcoma and hepatocellular carcinoma. Seminars in Liver Diseases. 4(2): 158-169.

Tamburro, C.H., L. Makk and H. Popper. 1984. Early hepatic histologic alterations among chemical (vinyl monomer) workers. Hepatology. 4(3): 413-418.

Tatrai, E. and G. Ungvary. 1981. On the acute hepatotoxicity of inhaled vinyl chloride. Acta Morphol. Acad. Sci. Hung. 29(2-3): 221-226.

Th'eriault, G., H. Iturra and S. Gingras. 1983. Evaluation of the association between birth defects and exposure to ambient vinyl chloride. Teratology. 27(3): 359-370.

Torkelson, R.R., F. Oyen and V.K. Rowe. 1961. The toxicity of vinyl chloride as determined by repeated exposure of laboratory animals. Am. Ind. Hyg. Assoc. J. 22: 354-361.

Ungvary, G., A. Hudak, E. Tatrai, M. Lorincz and G. Folly. 1978. Effects of vinyl chloride exposure alone and in combination with trypan blue - applied systematically during all thirds of pregnancy on the fetuses of CFY rats. Toxicolcgy. 11(1): 45-54.

U.S. EPA. 1975. Preliminary assessment of suspected carcinogens in drinking water. Interim Report to Congress, June, 1975. U.S. EPA, Washington, DC.

U.S. EPA. 1980. Ambient Water Quality Criteria for Vinyl Chloride. EPA 440/4-80-078. NTIS PB 81-117889.

U.S. EPA. 1983a. Review of Toxicologic Data in Support of Evaluation for Carcinogenic Potential of: Vinyl Chloride. Carcinogen Assessment Group, OHEA, U.S. EPA, Washington, DC.

U.S. EPA. 1983b. Reportable Quantity Document for Vinyl Chloride. ECAO, Cincinnati, OH.

U.S. EPA. 1984a. Examination of recent information concerning cancer risk associated with vinyl chloride. Memo from Robert McGaughy, Acting Director, Carcinogen Assessment Group to John Dadget, Director, Office of Air Quality Planning and Standards, Washington, DC.

U.S. EPA. 1984b. Health Effects Assessment for Vinyl Chloride. Environmental Criteria and Assessment Office, Cincinnati, OH. ECAO-CIN-H036.

U.S. EPA. 1984c. Technical Support Document and Summary Table for the Ranking of Hazardous Chemicals Based on Carcinogenicity. Carcinogen Assessment Group, OHEA, Washington, DC.

U.S. EPA. 1985. Reference Values for Risk Assessment. Environmental Criteria and Assessment Office, Cincinnati, OH. ECAO-CIN-477.

USITC (U.S. International Trade Commission). 1984. Synthetic Organic Chemicals. U.S. Production and Sales, 1983. USITC Publ. 1588. p. 259, 260.

Vainio, H. 1978. Vinyl chloride and vinyl benzene (styrene) - metabolism, mutagenicity and carcinogenicity. Chem.-Biol. Interact. 22(1): 117-124.

Veith, G.D., K.J. Macek, S.R. Petrocelli and J. Carroll. 1980. An evaluation of using partition coefficients and water solubility to estimate bioconcentration factors for organic chemicals in fish. In: Aquatic Toxicology, ASTM STP 707, J.G. Eaton, P.R. Parrish and A.C. Hendricks, Ed. American Society for Testing and Materials. p. 116-129.

Verburgt, F.G. and E. Vogel. 1977. Vinyl chloride mutagenesis in Drosophila melanogaster. Mutat. Res. 48(3-4): 327-336.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., New York. p. 1185.

Viola, P.L. 1970. Pathology of vinyl chloride. Med. Lavoro. 61: 174-180. (Cited in U.S. EPA, 1983b)

Viola, P.L., A. Bigotti and A. Caputo. 1971. Oncogenic response of rat skin, lungs, and bones to vinyl chloride. Cancer Res. 31: 516-522.

Wagoner, J.K., P.F. Infante and R.B. Apfeldorf. 1980. Toxicity of vinyl chloride and poly(vinyl chloride) as seen through epidemiologic observations. J. Toxicol. Environ. Health. 6(5-6): 1101-1107.

Wakeman, I.B. and H.R. Johnson. 1978. Vinyl chloride formation from the thermal degradation of poly(vinyl chloride). Polym. Eng. Sci. 18(5): 404-407.

Watanabe, P.G. and P.J. Gehring. 1976. Dose-dependent fate of vinyl chloride and its possible relationship to oncogenicity in rats. Environ. Health Perspect. 17: 145-152.

Watanabe, P.G., G.R. McGowan and P.J. Gehring. 1976a. Fate of 14C-vinyl chloride after single oral administration in rats. Toxicol. Appl. Pharmacol. 36(2): 339-352.

Watanabe, P.G., G.R. McGowan, E.O. Madrid and P.J. Gehring. 1976b. Fate of (14) vinyl chloride following inhalation exposure in rats. Toxicol. Appl. Pharmacol. 37: 49-59.

Watanabe, P.G., J.A. Zempel, D.G. Pegg and P.J. Gehring. 1978a. Hepatic macromolecular binding following exposure to vinyl chloride. Toxicol. Appl. Pharmacol. 44(3): 571-579.

Watanabe, P.G., J.A. Zempel and P.J. Gehring. 1978b. Comparison of the fate of vinyl chloride following single and repeated exposure in rats. Toxicol. Appl. Pharmacol. 44(2): 391-399.

Waxweiler, R.J., W. Stringer, J.K. Wagoner, J. Jones, H. Falk and C. Carter. 1976. Neoplastic risk among workers exposed to vinyl chloride. Ann. NY Acad. Sci. 271: 40-48.

Waxweiler, R.J., H. Falk, A. McMichael, J.S. Mallov and A.S. Grivas. 1977. A cross-sectional epidemiologic survey of vinyl chloride workers. NTIS PB-274193. 50 p.

Westrick, J.J., J.W. Mello and R.F. Thomas. 1984. The groundwater supply survey. J. Am. Water Works Assoc. 76: 52-59.

Wisniewska-Knypl, M. Justyna, J. Klimczak and J. Kolakowski. 1980. Monooxygenase activity and ultrastructural changes of liver in the course chronic exposure of rats to vinyl chloride. Int. Arch. Occup. Environ. Health. 46(3): 241-249.

Withey, J.R. 1976. Pharmacodynamics and uptake of vinyl chloride monomer administered by various routes to rats. J. Toxicol. Environ. Health. 1(3): 381-394.

Woldbaek, T. and P. Klaboe. 1978. The photochemical reaction of vinyl chloride with oxygen studied by IR spectroscopy. Spectrochim. Acta. Part A. 34: 481-487.

Zhang, J., S. Hatakeyama and H. Akimoto. 1983. Rate constants of the reaction of ozone with trans-1,2-dichloroethene and vinyl chloride in air. Int. J. Chem. Kinet. 15(7): 655-668.

APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in February and March, 1985. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. 486 p.

ACGIH (American Conference of Governmental Industrial Hygienists). 1985. TLVs: Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1984-1985. Cincinnati, OH. 116 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. 2878 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B. John Wiley and Sons, NY. p. 2879-3816.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2C. John Wiley and Sons, NY. p. 3817-5112.

Grayson, M. and D. Eckroth, Ed. 1978-1983. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., MA. 575 p.

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyons, France.

ITII (International Technology Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

NTP (National Toxicology Program). 1985. Toxicology Research and Testing Program. Chemicals on Standard Protocol. Management Status.

Ouellette, R.P. and J.A. King. 1977. Chemical Week Pesticide Register. McGraw-Hill Book Co., NY.

Sax, I.N. 1979. Dangerous Properties of Industrial Materials, 5th ed. Van Nostrand Reinhold Co., NY.

SRI (Stanford Research Institute). 1984. Directory of Chemical Producers. Menlo Park, CA.

U.S. EPA. 1982. Chemical Activities Status Report, 3rd ed. (EPACASR). Offices of Pesticides and Toxic Substances, Washington, DC. EPA 560/TIIS-82-002b.

U.S. EPA. 1983. Status Report on Rebuttable Presumption Against Registration (RPAR) or Special Review Process. Registration Standards and the Data Call in Programs. Office of Pesticide Programs, Washington, DC.

U.S. EPA. 1984. CSB Existing Chemical Assessment Tracking System. Name and CAS Number Ordered Indexes. Office of Toxic Substances, Washington, DC.

USITC (U.S. International Trade Commission). 1983. Synthetic Organic Chemicals. U.S. Production and Sales, 1982, USITC Publ. 1422. Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv., Resource Publ. 137. Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California. State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effect of Pesticides on Non-Target Species. PB-269605. Prepared for the U.S. EPA, Washington, DC.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. EPA 540/9-79-003. NTIS PB 80-196876. Office of Pesticide Programs, U.S. EPA, Washington, DC.

In addition, the following were obtained and reviewed:

Status Report 8EHQ-0982-0457
Status Report 8EHQ-0680-0345
FYI-OTS-0379-0026